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Diagnosis and management challenges of in-stent restenosis in coronary arteries

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Abstract

Over the course of the 3 decades, percutaneous coronary intervention (PCI) with stent implantation transformed the practice of cardiology. PCI with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents. Due to these favorable findings, DES was rapidly and widely adopted enabling more complex coronary interventions. Nevertheless, ISR remains a serious concern as late stent complications. ISR mainly results from aggressive neointimal proliferation and neoatherosclerosis. DES-ISR treatment continues to be challenging complications for interventional cardiologists.

Key words: Stent; In-stent; Restenosis; Percutaneous coronary intervention

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Core tip: Percutaneous coronary intervention with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents. However, ISR remains a serious concern as late stent complications. ISR mainly results from aggressive neointimal proliferation and neoatherosclerosis. DES-ISR treatment continues to be challenging complications for interventional cardiologists. This review focuses on pathogenesis, diagnosis and treatment options for ISR in the current era of advanced intravascular imaging and intervention.

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INTRODUCTION

Percutaneous coronary intervention (PCI) with stenting is currently the most widely performed procedure for the treatment of symptomatic coronary disease^[1]. Over the course of the 3 decades, PCI with stent implantation transformed the practice of cardiology. In large trials, drug-eluting stents (DES) have led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents (BMS)^[2]. Due to these favorable findings, DES was rapidly and widely adopted enabling more complex coronary interventions. Nevertheless, ISR remains a serious concern as late stent complications.

DEFINITION

ISR is defined as the gradual re-narrowing of a stented coronary artery lesion due to arterial damage with subsequent neointimal tissue proliferation^[3,4]. Angiographically IRS is a binary event defined as recurrent diameter stenosis at the stent segment more than 50% of the vessel diameter as determined by coronary angiography^[4]. The angiographic definition remains the main definition since it allows determination of ISR severity and morphological pattern. The clinical definition of ISR requires the presence of greater than 50% diameter in-stent stenosis and one of the following: Clinical symptoms of recurrent angina, objective signs of ischemia (EKG changes), positive coronary hemodynamic assessment with fractional flow reserve (FFR) less than 0.80, intravascular ultrasonography (IVUS) minimum cross-sectional area less than 4 mm² (6 mm² for left main), or restenosis with $\geq 70\%$ reduction in lumen diameter even in the absence of clinical symptoms or signs.

CLASSIFICATION

Multiple classification systems have been identified to address the severity of ISR. Mehran system^[5] is a morphologic classification of ISR lesions in to four patterns. Pattern I (focal) is ISR (≤ 10 mm in length) lesion within the stent, pattern II (diffuse) is ISR greater than 10 mm within the stent, pattern III (proliferative) is ISR greater than 10 mm extending outside the stent, and pattern IV (occlusion) is totally occluded ISR. This classification system predicts the need for repeat revascularization after intervention (19%, 35%, 50%, and 98%, respectively)^[5]. American College of Cardiology/American Heart Association lesion

classification has been also validated in patients with ISR^[6]. Type A lesions had a probability of success of more than 85% and a low risk of acute occlusion. Type B lesions had a probability of success of between 60% and 85% and a moderate risk of abrupt occlusion. Finally, type C lesions had a probability of success of less than 60% and a high risk of abrupt occlusion following the procedure (Table 1). Lesions B2 and C have been reported to be frequently associated with suboptimal acute results with a higher restenosis rate and poorer long-term clinical outcomes^[7].

INCIDENCE

In general, rates of ISR range from 3% to 20% with drug-eluting stents and 16% and 44% with BMS. This occurs mostly between 3 to 20 mo after stent placement^[3,8]. The incidence of ISR depends on the definition, stent type, location, patient comorbidities and lesion complexity (*i.e.*, lesion length, vessel size, and bifurcation lesions). The introduction of DES has significantly reduced the occurrence of neointimal proliferation, which is considered the main mechanism for ISR. The decrease in ISR was translated into decreased clinical need for subsequent repeat revascularization^[9-11]. A meta-analysis of 38 randomized controlled trials with more than 18000 patients showed significant reduction in TLR with both sirolimus-eluting stent (SES) and paclitaxel-eluting stents (PES) compared with BMS^[10]. However, due to the complexity of ISR beyond device and stent design, the rates of ISR in both BMS and DES are still relatively high^[12]. Routine angiographic surveillance 6 to 8 mo after stent implantation was done in one study that revealed ISR rates of 30.1%, 14.6%, and 12.2% for BMS, first-generation DES, and second-generation DES, respectively^[13].

Bare-metal stents ISR

Despite relatively high restenosis rates, bare-metal stents are still frequently used in clinical practice during PCI^[14]. This is related to unaffordable prices of DES and more importantly, lower risk of bleeding due to shorter duration of dual antiplatelet therapy (DAPT) that is required after BMS compared with DES. BMS-ISR causes a significant therapeutic burden in current clinical practice. One pooled analysis reported a one-year TLR and TVR rates after BMS of 12% and 14.1% respectively^[15,16]. Clinical restenosis was evident within 6-12 wk after BMS implantation^[16]. Beyond 1 year, rate of BMS restenosis is negligible and most stenting events are related to disease progression in vessel segments other than the stented lesion^[16].

Drug-eluting stents ISR

Restenosis rate of DES increased in the recent years due to expanded use to include high-risk patients with complex coronary lesions. The DES-ISR rate has been reported in 3%-20% depending on DES type, the duration of follow-up, and the complexity of the lesions

Table 1 ACC/AHA lesion-specific classification of the primary target stenosis

Lesion type		Lesion characteristic according to AHA/ACC classification				
Type A lesions	Discrete (< 10 mm length)	Concentric	Readily accessible	Non angulated segment < 45°	Smooth contour	Little or no calcification
	Less than totally occlusive	Not ostial in location	No major branch involvement	Absence of thrombus		
Type B1 lesions	Tubular (10-20 mm length)	Eccentric	Moderate tortuosity of proximal segment	Moderately angulated segment, 45°-90°	Irregular contour	Moderate to heavy calcification
	Total occlusion < 3-mo-old	Ostial in location	Bifurcation lesions requiring double Guidewires	Some thrombus present		
Type B2 lesions	Two or more "B" characteristics					
Type C lesions	Diffuse (> 2 cm length)	Total occlusion > 3-mo-old	Excessive tortuosity of proximal segment	Extremely angulated segments, > 90°	Inability to protect major side branches	Degenerated vein grafts with friable lesions

in which the stents were placed^[3]. When compared with BMS, DES is associated with lower ISR. At one-year follow up, SES markedly reduced the incidence TLR from 16.6% to 4.1% when compared with BMS^[17]. For first-generation DES, j-Cypher registry of 12812 patients who received SES, the TLR rate was 7.3% at 1 year, and 15.9% at 5 years^[18]. Ischemia-driven TLR was also the same in patients randomly assigned to SES or PES (13.1% vs 15.1%) in the SIRTAX LATE study^[19]. Second generation stents have been associated with lower death and myocardial infarction compared with first-generation DES. However, zotarolimus-eluting stent (ZES) found to be noninferior to PES for TVR at 1 and 5 years^[20]. In a pooled analysis of multiple studies comparing everolimus-eluting with ZES, the rates of TVR at up to five years of follow-up were 6.3% and 5.0%, respectively^[21].

PREDICTORS OF IN-STENT RESTENOSIS

Patient comorbidities, lesion characteristic, and procedural characteristics are the main predictors of ISR.

Patient characteristics

Patient characteristics and comorbidities that are associated with higher rate of ISR include; metal allergy, local hypersensitivity reactions with immunologic and inflammatory response to the drug or the polymer, age, female gender, diabetes mellitus, chronic kidney disease (including hemodialysis), and multivessel coronary artery disease^[3,22,23].

Lesion characteristics

Lesion characteristics associated with ISR include; lesion length, smaller reference artery diameter, ostial lesion, initial plaque burden and residual plaque after implantation. In contrast with BMS, DES tends to have a more focal pattern of ISR, except in diabetics, where the ISR tends to be more confined to the stent edges^[24,25]. Focal ISR (Mehran pattern I) has been associated with a lower rate of ISR recurrence than nonfocal (Mehran pattern > I) ISR^[25].

Procedural characteristics

Operator and technique dependent characteristics include stent undersizing, incomplete lesion coverage, stent under expansion, and malapposition. Mechanical properties of stents that may lead to recoil because of loss of radial force, stent fractures, and altering increase in shear stress are all associated with higher rates of ISR. For every 10 mm of excess stent length beyond lesion has been independently associated with increased post-procedural percent diameter stenosis by 4% and increased TLR at 9 mo (OR = 1.12, 95%CI: 1.02-1.24)^[26-29]. Stent fracture, on the other hand, can trigger focal ISR or thrombosis^[30-32] which can result in a reduction in drug delivery at the breakage point of the stent. Stent fracture occurs more frequently in the right coronary artery, overlapping stents, longer stents, SESs (because of the ridged closed cell structure), and excessively tortuous angulated vessels^[33]. Malapposition, also known as incomplete stent apposition (ISA), is defined as the absence of contact between stent struts and the vessel wall not overlying a side branch. Malapposition seems to be related to procedural technique due to under-sizing the stent, use of low deployment pressures, and severely calcified lesions, which do not allow for homogenous stent expansion^[34]. Oversized stents can also lead to extensive trauma to the vessel wall and increased proliferative reaction^[35]. Geographic miss occurs when the stent does not fully cover the injured or diseased segment of the artery (axial miss) or the ratio of balloon to artery size is less than 0.9 or greater than 1.3 (longitudinal miss). Geographic miss is associated with increased risk of TLR and MI at 1 year^[36]. DESs decrease neointimal growth. As a result, geographic miss or strut fracture may be larger factors of ISR in DESs compared with BMSs^[12].

PATHOGENESIS

The main mechanism of ISR following stent implantation is neointimal tissue proliferation because of arterial wall damage^[21,22]. Neointimal tissue proliferation could be focal or distributed uniformly along the

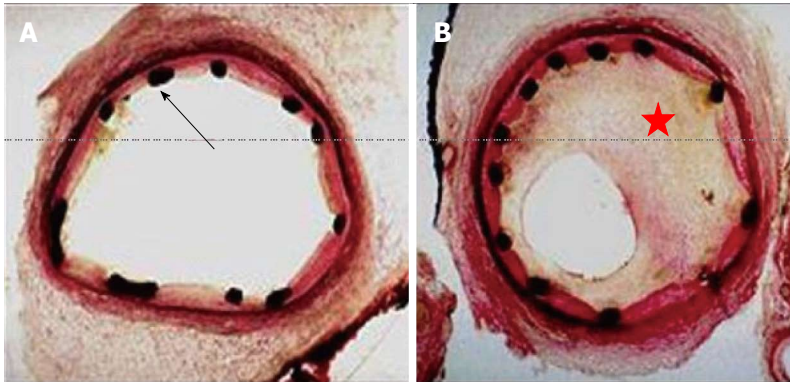


Figure 1 The figure showing cross-section of coronary artery immediately after implantation of a bare metal stent black dots represent the stent struts (red arrow) (A); the figure showing significant in-stent restenosis with neointimal hyperplasia (red star) 6 mo after the implantation of a bare metal stent (B).

length of the stent (Figure 1). ISR, which happens early within days of stent deployment, is due to elastic recoil and relocation of axially transmitted plaque. The causes of late (weeks to months) ISR commonly are reorganization of thrombus, neointima formation and remodeling^[37].

Neointimal hyperplasia is another contributing factor to ISR. The stimulation of neointima formation happens due to injury to the vessel during the PCI and stent deployment. A cascade of events are triggered by the intimal and medial damage, leading to proliferation and migration of vascular smooth muscle cells, extracellular matrix formation which ultimately activates the coagulation-fibrinolysis system^[38]. The local inflammation can lead to the development of neointimal hyperplasia characterized by accumulation of lipid-laden foamy macrophages within the neointima with or without a necrotic core formation and calcification, which can occur years after stent placement^[39]. Neointimal hyperplasia is associated with a higher proportion of in-stent atherosclerotic plaque, which could explain unstable symptoms and myocardial infarction presentation of patients with ISR years after PCI. The incidence of neointimal hyperplasia was significantly greater in DES compared with BMS (31% vs 16%, $P < 0.001$)^[40]. Younger age, longer implant durations, SES usage, PES usage and underlying unstable plaques, are independent risk factors for neointimal hyperplasia^[14,40].

CLINICAL PRESENTATION

Due to the gradual and slow progression of ISR compared with stent thrombosis, majority of ISR presents as progressive recurrent angina^[40]. The time for symptoms to develop due to DES-ISR is 3 to 12 mo after stent placement^[41]. BMS stent on the other hand develop ISR symptoms sooner with reported average period of 6 mo post-PCI^[42]. BMS-ISR presented as MI in 3.5%-20% of patients^[43]. DES-ISR is similar to that of BMS with approximately 16%-66% of patients presenting with unstable angina and 1%-20% with MI^[44,45].

ANATOMIC ASSESSMENT

Routine surveillance

Routine angiographic surveillance is not recommended

because it has been shown to increase the rates of occlusive restenosis.

Intravascular ultrasonography

IVUS is considered a fundamental intracoronary imaging modality to assess ISR. The stent and procedures characteristics can be readily assessed as contributing mechanism of ISR using IVUS^[35]. IVUS delineate external elastic lamina behind the stent struts very well, which provides valuable insights on vessel sizing for optimization of stent expansion (Figure 2F and G). IVUS does help detect the presence of neointimal hyperplasia obstructing the stent, stent underexpansion, stent fracture, or edge restenosis. In addition, it can provide insights into optimal vessel sizing for choosing the appropriate stent size (Figure 2K and L). However, IVUS has limited axial resolution (150 μm), which makes neointimal interface hard to define^[12].

Optical coherence tomography

Optical coherence tomography (OCT) provides better axial resolution (15 μm), allowing better resolution of the vessel lumen, neointimal tissue, and stent struts distribution. The morphology of ISR can be identified using OCT which could show macrophage infiltration, necrotic core, in-stent calcification and neointimal plaque rupture^[46,47]. The weakness of the OCT resides in the poor tissue penetration, which cause poor visualization of the residual plaque that is beyond the stent^[12].

HEMODYNAMIC ASSESSMENT

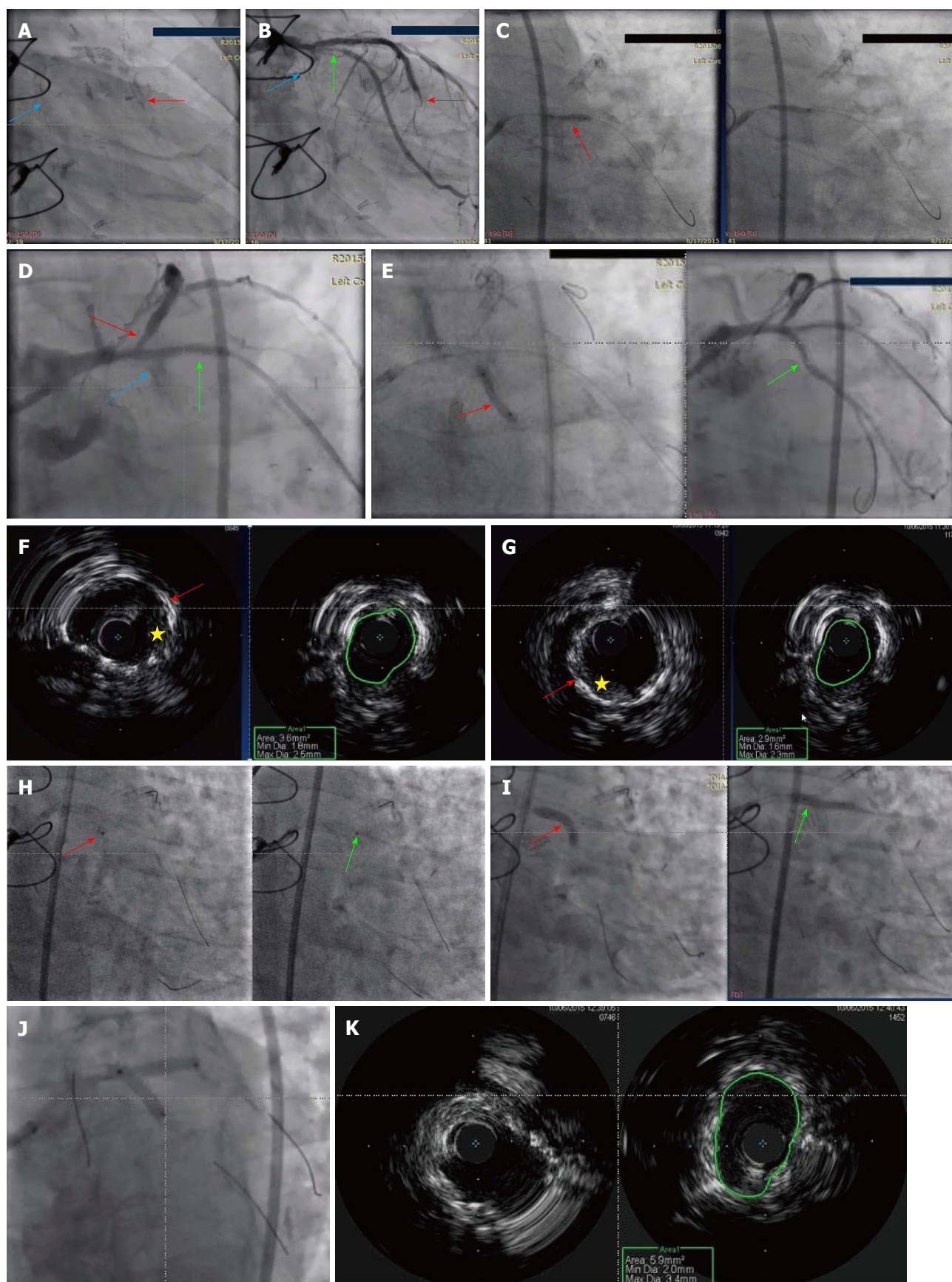
Fractional flow reserve

FFR has been validated for clinical decision making in patients with ISR. The clinical outcome of patients with ISR with deferred interventions based on a FFR > 0.75 is excellent^[48]. This diagnostic strategy is useful in controversial cases with angiographically moderate or inconclusive ISR.

TREATMENT

Balloon angioplasty

Balloon angioplasty (BA) is one of the earliest interventions that were used to treat ISR by displacing in-



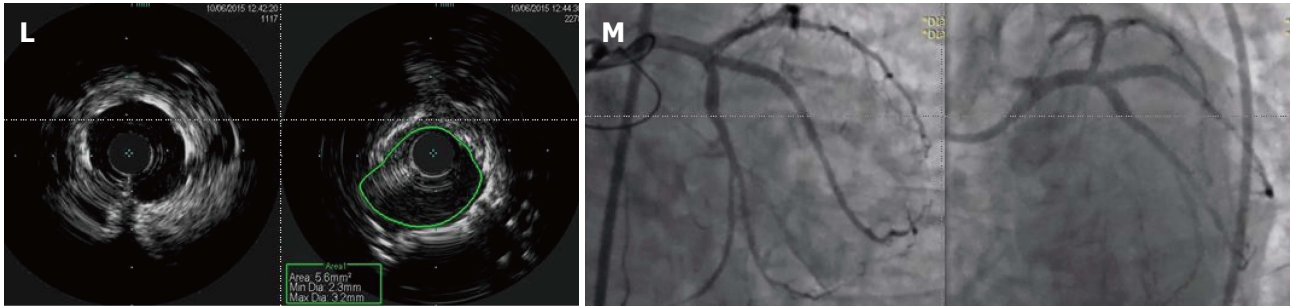


Figure 2 Sixty-seven-year-old man presented with increasing chest pain at rest. He has past medical history significant for coronary artery disease with PCI and coronary artery bypass grafting. He had PCI with (3.0 mm × 12 mm) DES to LCx, (2.5 mm × 16 mm) DES to RI and (2.5 mm × 16 mm) DES to obtuse marginal a year prior to his presentation. The left internal mammary artery to LAD is patent, however, he is known to have occluded SVG to RI and SVG to first diagonal (D1). Given his increasing chest pain, coronary angiogram was done. A: Coronary stents before contrast injection in LAD (red arrow), LCx (blue arrow); B: Coronary angiogram of the same patient showing severe proximal LCx ISR (blue arrow) with no flow, severe proximal RI ISR (green arrow) with slow flow, and mid LAD severe ISR (red arrow); C: Dilation of the RI coronary artery with 2.5 mm × 22 mm NC balloon with 22 atm inflation pressures was done; D: Coronary angiogram showing the proximal RI ISR (green arrow) post balloon dilation. Red arrow shows severe proximal LAD stenosis with poor flow. LCx has completely occluded ISR (blue arrow); E: The left circumflex ISR lesion (red arrow) was wired and with balloon dilation the flow was restored in the LCx (green arrow); F: IVUS imaging of the underexpanded stent in the proximal LCx lesion. Left panel shows stent struts (red arrow) with evidence of neointimal hyperplasia (yellow star). The right panel shows small stent CSA of only 3.6 mm² which is below the target 5 mm² in Asians and 6 mm² in non-Asians; G: IVUS imaging of the underexpanded stent in the proximal ramus coronary artery. Left panel shows severely under-expanded stent (red arrow) with evidence of neointimal hyperplasia (yellow star). The right panel shows small stent CSA of only 2.9 mm²; H: Excimer Laser Coronary Angioplasty treatment of LCx (left panel - red arrow) and ramus artery (right panel - green arrow) using 0.9 mm coronary laser and the heparinized flush technique. Laser catheter was advanced slowly at 0.2-0.5 m/s during laser emission with careful monitoring of heart rate and blood pressure. Vessel injury such as perforation, dissections and acute closure are the main side effects; I: Post laser balloon dilation with (3.5 mm × 20 mm) NC balloon of both LCx (red arrow) and ramus (green arrow) arteries; J: Sequential kissing stenting technique in the proximal LCx and ramus arteries with DES 3.5 mm × 18 mm in Ramus and 3.5 mm × 15 mm in LCx; K: IVUS imaging of the stent in the proximal LCx coronary artery that shows good expansion of the stent with great increase in CSA to 5.9 mm²; L: IVUS imaging of the stent in the proximal ramus coronary artery that shows good expansion of the stent with great increase in CSA to 5.6 mm²; M: TIMI III flow was achieved in the LCx and Ramus coronary arteries without any compromise of LAD. PCI: Percutaneous coronary intervention; DES: Drug-eluting stents; LCx: Left circumflex; RI: Ramus intermedius; LAD: Left anterior descending artery; SVG: Saphenous vein graft; ISR: In-stent restenosis; NC: Non-compliant; IVUS: Intravascular ultrasound; CSA: Cross-sectional area.

stent tissue from the lumen in axial and longitudinal direction to the outer portion of the vessel wall as well as further expanding the stent^[49] (Figure 2). This intervention could be useful in focal ISR. The outcome of BA for focal ISR. However, during balloon inflation, slippage or watermelon seeding can occur, leading to edge-related complications. Cutting or scoring balloons can help minimize this, but also have limitations in delivery through stented regions or distal areas^[50]. Lateral blades or atherotomes anchor the balloon in the lesion and minimize slippage^[51]. Progressive balloon dilations and small/short balloons can also prevent side effects from balloon slippage^[52]. One of the limitations of BA is that subacute tissue re-intrusion back to the lumen tends to occur within minutes after the last balloon inflation. This explains the early lumen loss phenomenon detected in BA studies in this setting, a finding also associated with subsequent recurrent restenosis.

Vascular brachytherapy

Brachytherapy inhibits neointimal formation within the stent, but not the stent edges, by delivering radiation to the areas of ISR. Brachytherapy effectively suppressed the proliferative response and significantly reduced clinical and angiographic restenosis rates (Figure 3C). Both beta and gamma radiation sources could achieve major reductions in the angiographic restenosis rates^[53]. Gamma emitters had profound tissue penetration, whereas beta emitters had less tissue penetration

(Figure 3E). Randomized clinical trials in patients with ISR demonstrated the superiority of brachytherapy compared with conventional BA or atheroablative techniques^[53-55]. Adding an extra layer of metal to treat DES or BMS-ISR is not ideal and will continue to place patients at future risk for ISR. Therefore, DEB and vascular brachytherapy are better options compared with DES. Vascular brachytherapy is available in few centers in the United States and is used primarily for recurrence of DES-ISR, but logistic issues and lack of radiation oncology support impede its uses. Therefore, restenting with second-generation DES became the default therapy for DES-ISR.

Excimer laser angioplasty

Excimer laser angioplasty (ELA) produces monochromatic light energy, which generates heat and shock waves that disrupt plaque (Figure 2H). Mehran *et al.*^[56] compared results of ELA vs rotational atherectomy (RA), both followed by percutaneous transluminal coronary angioplasty (PTCA). 119 patients with 158 ISR lesions were treated with ELA plus PTCA and 130 patients with 161 ISR lesions were treated with RA plus PTCA. Volumetric IVUS analysis showed a greater reduction in intimal hyperplasia volume after RA than after ELA (43 mm³ vs 19 mm³, $P < 0.001$). However, the 1-year TLR rates were similar: 26% with ELA plus PTCA vs 28% with RA plus PTCA ($P =$ nonsignificant). ELA is not currently a well-accepted treatment for ISR, but the ultimate role of this therapy

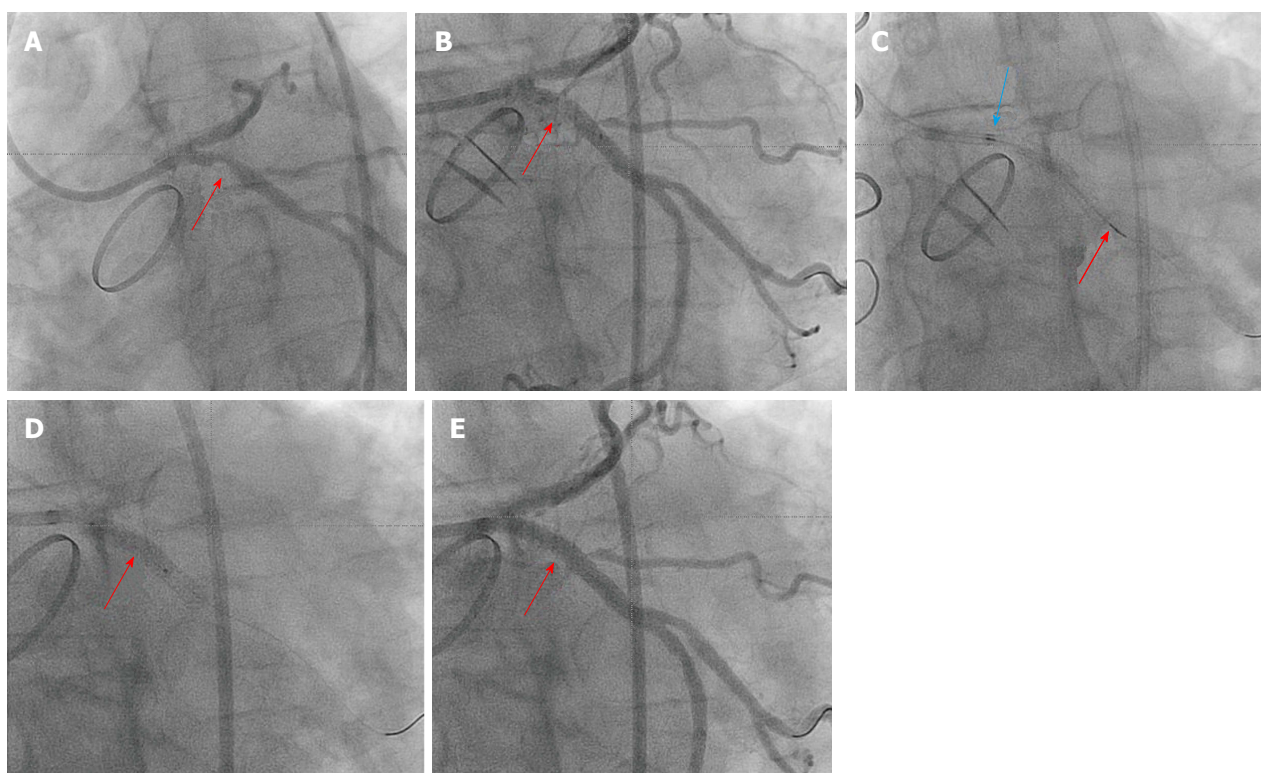


Figure 3 Fifty-five-years-old caucasian male with mantle cell radiation for Hodgkin's lymphoma complicated with radiation heart valve disease with severe aortic valve stenosis status post mechanical aortic valve replacement surgery. Few years later he presented with chest pain and had PCI to the proximal LAD and LCx with DES. However, both few months later he developed ISR and underwent another PCI with DES to the proximal LAD and LCx. Patient was referred for vascular brachytherapy for the treatment of ISR of the LCx due to increased chest pain at rest and recurrent ISR of proximal LCx. A: Coronary angiogram showing 90% focal proximal LCx ISR (red arrow); B: Balloon angioplasty of the proximal LCx lesion (red arrow) to prepare the lesion before brachytherapy delivery; C: Coronary angiogram showing the Novoste Beta-Cath™ System that was used to deliver a source train that contains 12 individual radioactive seeds (blue arrow to red arrow). Once properly positioned, 23 Gy from the center of the source center was prescribed. The patient was monitored during the dwell time which required 4 min and 49 s; D: Another balloon angioplasty was done after the radioactive seeds are pulled from LCx; E: Final TIMI-III flow in the LCx. PCI: Percutaneous coronary intervention; LAD: Left anterior descending artery; LCx: Left circumflex; DES: Drug-eluting stents; ISR: In-stent restenosis.

is still unclear.

Drug-eluting balloon angioplasty

It was proposed that repeat stenting for ISR raises concerns for creating multiple stent layers. Therefore, the use of DEB angioplasty should minimize the metal layer and eventually decrease future ISR. For that purpose, multiple randomized studies have been done to evaluate the efficacy and durability of DEB compared with DES in treating BMS or DES-ISR. Few studies have shown that DEB is non-inferior to DES for BMS and DES-ISR^[52-61]. However, none of these studies have been powered for clinical endpoints. DEB is currently not available for use in the United States. In addition, their use has been associated with issues that may limit their use mostly related to the use of paclitaxel and potential of particulates showering to the distal vessel bed, as well as the high profile of the device. Comparison of DEB with DES for treatment of ISR will be discussed in the following section.

Drug-eluting stents

Balloon angioplasty alone carries a high risk of recurrent stenosis, especially in diffuse and/or severe ISR^[44,62,63].

The randomized trials Paclitaxel-eluting Stents vs Brachytherapy for In-stent Restenosis (TAXUS V ISR) and Sirolimus-eluting Stents vs Vascular brachytherapy (SISR) trial showed better outcomes for DES compared with brachytherapy^[64,65]. Two major randomized trials compared DES with DEB for patients with ISR. The ISAR-DESIRE 3 trial randomized 402 patients with ISR in DES to paclitaxel-eluting balloon (PEB) vs first generation DES (PES) vs balloon angioplasty^[52]. At a median follow-up of 3 years, the risk of TLR was similar with PEB vs PES (HR = 1.46, 95%CI: 0.91-2.33, $P = 0.11$) and lower with PEB vs balloon angioplasty (HR = 0.51, 95%CI: 0.34-0.74, $P < 0.001$). The risk of death/MI was lower, but not statistically significant, with PEB vs PES (HR = 0.55, 95%CI: 0.28-1.07, $P = 0.08$). This finding was driven by a lower risk of death (HR = 0.38, 95%CI: 0.17-0.87, $P = 0.02$). The risk of death/MI was similar with PEB vs balloon angioplasty (HR = 0.96, 95%CI: 0.46-2.0, $P = 0.91$). Using the second generation DES, Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloon vs Everolimus-Eluting Stent (RIBS IV) trial, evaluated the comparative efficacy of DEB and EES in patients presenting with DES-ISR^[66,67]. A total of 309 patients with DES-ISR

were randomly allocated to DEB, or second generation DES (EES) patients in the EES arm had a significantly larger minimal lumen diameter (2.03 ± 0.7 mm vs 1.80 ± 0.6 mm, $P < 0.01$) net lumen gain (1.28 ± 0.7 mm vs 1.01 ± 0.7 mm, $P < 0.01$), and lower percent diameter stenosis ($23\% \pm 22\%$ vs $30\% \pm 22\%$, $P < 0.01$) and binary restenosis rate (11% vs 19% , $P = 0.06$), compared with patients in the DEB arm. At the 1-year clinical follow-up (100% of patients), the main clinical outcome measure (composite of cardiac death, myocardial infarction, and target vessel revascularization) was significantly reduced in the EES arm (10% vs 18% , $P = 0.04$, HR = 0.58, 95%CI: 0.35-0.98), mainly driven by a lower need for target vessel revascularization (8% vs 16% , $P = 0.035$).

A meta-analysis looked into treatment of ISR comparing DEB, DES, and BA reported that treatment with DEB had a trend toward better outcomes than with DES^[68-72]. The risk of TLR was lower in patients treated with DEB (OR = 0.22, 95%CI: 0.10-0.42) or DES (OR = 0.24, 95%CI: 0.11-0.47) than in those treated with BA. In a comparison of DEB and DES, the risk of TLR (OR = 0.92, 95%CI: 0.43-1.90) was similar. The risk of major adverse cardiac events, which was mainly driven by TLR, was also significantly lower in the DEB and DES groups (OR = 0.28, 95%CI: 0.14-0.53) than in the BA group, but it was similar between the DEB and DES groups (OR = 0.84, 95%CI: 0.45-1.50). For TLR, the probability of being ranked as the best treatment was 59.9% (DEB), 40.1% (DES), and 0.1% (BA).

There is no clear evidence on which type of DES should be used to treat ISR of a DES. Some experts argue that using a different type of DES helps to overcome drug resistance, but no strong data support this practice. A recently published network meta-analysis addressed the question of which strategy is preferred for the treatment of ISR, with the primary outcome defined as the percent diameter stenosis at angiographic follow-up^[73]. This analysis suggested that PCI with second-generation DES (EES) was the most effective treatment, whereas percutaneous coronary intervention with DEB was ranked as the second most effective treatment but without significant differences from first-generation DES. Two additional similar design meta-analyses have reported similar findings suggesting second generation DES as treatment of choice for BMS and DES-ISR^[74,75]. As a result, the 2009 update of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline update for PCI and the 2005 European Society of Cardiology Task Force recommend DES for ISR whether the initial stent was BMS or DES^[76-78].

A recently published pooled analysis of the RIBS V and RIBS IV compared the efficacy of EES in patients with BMS-ISR and DES-ISR^[79-82]. The study detected clinical and morphological differences of ISR in BMS vs DES, including for the later more focal ISR pattern and delayed onset of presentation. Nevertheless, the

outcome of the patients with DES restenosis was less favorable with regard to the angiographic indices, including lumen diameter post procedure and at follow-up. DES-ISR group treated with EES had both increased mortality and need for target vessel revascularization as compared with BMS-ISR group at one year follow up. The authors conclude that EES provides favorable outcomes in patients with ISR and that the results of EES are less satisfactory in patients with DES-ISR than in those with BMS-ISR.

CONCLUSION

In-stent restenosis remains a prevailing clinical problem. The substrate of ISR includes a pathological spectrum ranging from smooth muscle cell proliferation to neoatherosclerosis. Optimal stent deployment, utilization of imaging-guided implantation by IVUS or OCT, adequate coverage of the lesion, verifying stent expansion and apposition to the vessel wall and minimal use of BMS are considered the main strategies to decrease ISR. Based on the currently available literature, the use of BMS should be minimal in clinical practice and replaced with second generation DES. For patients presenting with first ISR, vascular brachytherapy should be considered in patients with focal ISR, or high bleeding risk or requiring DAPT interruption. 2nd generation DES should be a second line therapy to avoid adding an extra layer of metal to treat DES. For patients presenting with recurrent ISR, second generation DES have better long-term outcomes specially if combined with DEB. DEB should be used as first line therapy for bifurcation restenosis to prevent excess metal at the carina.

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Cardiovascular involvement in celiac disease

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ingestion of gluten protein, which is found in wheat, rye, and barley grains, and results in both small intestinal manifestations, including villous atrophy, as well as systemic manifestations. The main treatment for the disease is a gluten-free diet (GFD), which typically results in the restoration of the small intestinal villi, and restoration of other affected organ systems, to their normal functioning. In an increasing number of recently published studies, there has been great interest in the occurrence of alterations in the cardiovascular system in untreated CD. Herein, published studies in which CD and cardiovascular terms appear in the title of the study were reviewed. The publications were categorized into one of several types: (1) articles (including cohort and case-control studies); (2) reviews and meta-analyses; (3) case studies (one to three patient reports); (4) letters; (5) editorials; and (6) abstracts (used when no full-length work had been published). The studies were subdivided as either heart or vascular studies, and were further characterized by the particular condition that was evident in conjunction with CD. Publication information was determined using the Google Scholar search tool. For each publication, its type and year of publication were tabulated. Salient information from each article was then compiled. It was determined that there has been a sharp increase in the number of CD - cardiovascular studies since 2000. Most of the publications are either of the type "article" or "case study". The largest number of documents published concerned CD in conjunction with cardiomyopathy (33 studies), and there have also been substantial numbers of studies published on CD and thrombosis (27), cardiovascular risk (17), atherosclerosis (13), stroke (12), arterial function (11), and ischemic heart disease (11). Based on the published research, it can be concluded that many types of cardiovascular issues can occur in untreated CD patients, but that most tend to resolve on a GFD, often in conjunction with the healing of small intestinal villous atrophy. However, in some cases the alterations are irreversible, underscoring the need for CD screening and treatment when cardiovascular issues arise of unknown etiology.

Abstract

Celiac disease (CD) is an autoimmune response to

Key words: Cardiovascular; Celiac disease; Gluten;

Heart; Vascular

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Core tip: Celiac disease (CD) is a public health concern suffered by about 1% of the population worldwide. It often goes undetected even in developed countries, owing to the varied and occult presentation which can make diagnosis difficult. Untreated, systemic manifestations including cardiovascular ailments can occur. In this review, information concerning the cardiovascular involvement in CD patients is described and discussed. Treatment of CD patients with a gluten free diet can reverse some, but not all of the cardiovascular involvement. Thus the need for prompt diagnosis and treatment.

Ciaccio EJ, Lewis SK, Biviano AB, Iyer V, Garan H, Green PH. Cardiovascular involvement in celiac disease. *World J Cardiol* 2017; 9(8): 652-666 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/652.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.652>

INTRODUCTION

Celiac disease (CD) is characterized by an immunologic response to gluten, which often results in diffuse inflammatory damage to the small intestinal mucosa, and malabsorption of nutrients^[1]. CD is of special interest among chronic diseases due to several factors: (1) it is associated with specific comorbidities; (2) it involves a compromised absorption of nutrients; and (3) a gluten-free diet (GFD) is currently the main long-term treatment^[2]. Studies have shown that certain cardiovascular maladies, including cardiomyopathy, myocarditis, arrhythmias, and premature atherosclerosis, are more prevalent in individuals with CD as compared to individuals without the disease^[3,4]. In this article, published works concerning the effects of CD on the cardiovascular system, and the risk of cardiovascular disease, are reviewed. The method of some previous analyses is followed to quantitatively characterize the published articles^[5-7], and to then compile the most salient information for review.

RESEARCH

The Google Scholar search tool was used to find associations between CD and the heart and vascular systems. Keywords pertaining to the heart and vascular system, tabulated in Table 1, were used for search in conjunction with "celiac disease", "coeliac disease", or "gluten". The searches were limited to the co-detection of these terms in the publication title, which is suggestive of the importance of the keywords. The cardiovascular keywords used for

search were derived from encyclopedic descriptions of the heart, vascular, and cardiovascular systems. Under these headings, all relevant terms were extracted as keywords. They were categorized as heart terms and vascular terms. The format used for search in Google Scholar was, for example: (1) allintitle: "celiac disease" "myocardial"; (2) allintitle: "coeliac disease" "myocardial"; and (3) allintitle: "gluten" "myocardial", where the results for the three forms of expression pertaining to CD were then combined. Heart and vascular keywords, tabulated in Table 1, were then combined to form summary topics for analysis. The number of CD/cardiovascular publications per year was then graphed for all of the summary topics.

The type of published document was also recorded for each keyword entry. Each citation used was categorized by type of published documentation as shown in Table 2. There are six possible publication types according to the list. All published documents were categorized as one of the types noted in Table 2. Graphical displays were utilized to separately show the number of CD/cardiovascular documents of each type noted in Table 2 that were published per year. Then for each of the summary topics, the total number of publications of each type in Table 2 were compiled. Also for each of the summary topics, the total number of studies and the mean publication year of the studies for the journals the studies were published in were tabulated. The essential points in each study were then condensed and described in review form, in separate sections, for each of the summary topics.

PUBLICATION SUMMARY STATISTICS

In Figure 1 is presented a graph of the number of publications per year in which CD and cardiovascular terms appeared. The earliest studies in which CD was investigated for cardiovascular function were published in 1970. However until the year 1998, only a handful of such studies were published, after which there began a substantial increase in the publishing of CD/cardiovascular studies. Although there were fluctuations in the number of studies in the 2000s and 2010s, the overall trend was a sharp upward swing in published studies. The data for 2017 only includes the first few weeks of the year.

The number of studies for selected types that was published per year is shown in bar graph form in Figure 2. The results are shown for articles (cohort), case studies, abstracts, and letters, and review and editorial publications. Many of the CD/cardiovascular published studies were either articles or case studies. As for graphs of the total studies published that were shown in Figure 1, the graphs of individual published document types in Figure 2 begin to exhibit substantial increases about the year 2000. There were also a number of abstracts and case reports published in the late 1980s and 1990s, as is notable in the case reports

Table 1 Cardiovascular terms used for search in the study

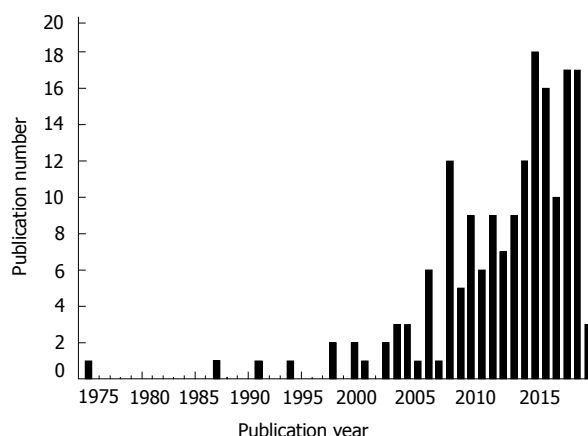
Heart terms	Vascular terms
Afterload, preload	Angiogenesis
Arrhythmia, rhythm	Aorta, aortic
Atrial, atrium	Arterial, arteries, artery
Atrioventricular	Arteriosclerosis, atherosclerosis
Bachmann's	Atherogenesis, atherogenic
Cardiac, cardio	Blood pressure
Cardiologist	Cardiovascular
Cardiomyopathies, cardiomyopathy	Circulatory
Congenital	Circumflex
Contractility	Coronary
Depolarization	Embolism
Effusion	Haemoptysis, hemoptysis
Ejection	Hemorrhage
Electromechanical	Haemodynamics, Hemodynamics
Endocardium, epicardium	Haemosiderosis, hemosiderosis
Fibrillation	Stroke
Foramen ovale	Thrombosis, thromboembolism
Frank-Starling	Vascular
Heart	Vein, veins
Infarction	Vena cava
Ischaemic, ischemic	Venous
Mitral	Venule, venules
Myocardial, myocardium	
Myocarditis	
Myocyte	
Pericardial, pericardium	
Purkinje	
QT	
Septum	
Sinoatrial	
Stenosis	

Table 2 Categories of published documents

Type	Description
Articles	Includes research articles, cohort studies and case control studies
Reviews	These included reviews of the literature and meta-analyses
Case studies	Limited to $n = 1-3$ patients in the study
Letters	These could include comments on other articles as well as case reports in letter form
Abstracts	When no full paper had been published, abstracts were included in the references
Editorials	These were typically comments on papers published in the same journal issue

graph in Figure 2. There are only a few review and editorial publications to date, but they are recent.

Based on all of this data, in Table 3 are provided, for each document type, the number of published studies for each topic, with the totals for all articles shown in the last row. Most of the published works are either articles (74) or case studies (62). There are also substantial numbers of letters (23) and abstracts (20). The totals for each term are given to the right in the table. The sum total, 190, is greater than the number of cited articles in this review, 180, because a particular citation could be used in more than one review topics

**Figure 1 Overall published studies on celiac disease/cardiovascular by year.**

section. Furthermore, several citations used in the Introduction were not cardiovascular studies and were not included in Table 3. A number of topics were particularly of interest for CD/cardiovascular publishing. These include papers on CD and cardiomyopathy (33 studies), thrombosis (27), cardiovascular risk (17), atherosclerosis (13), stroke (12), and arterial function and ischemic heart disease (11 each). In Table 4 are shown keyword terms and total number of studies, and median (range) study year of the journal. The median year for all of the studies is 2004 or later, except for the term "haemodynamics" (1998). Thus the possible connection between CD and "haemodynamics" tended to be investigated at earlier dates, as compared with other cardiovascular conditions.

Compilation of the celiac disease - cardiovascular literature

In this section, the study results for each keyword of Table 1 are combined into summary topics, to show the general consensus and trends for CD/cardiovascular publications. Thus the most pertinent information from all studies belonging to a particular cardiovascular term was collated by topic. The total number of studies (#) and median and range in years (median year) are shown for published studies concerning each topic. The terms are separated and noted as belonging to vascular or heart categories, followed by cardiovascular risk assessment.

Vascular - arterial function [# = 11, median year = 2014 (2011-2016)]

Arterial function is of great concern in CD. Measurements to quantify alterations are made using echocardiography and pulse wave velocity^[8,9]. In untreated CD, aortic function can deteriorate, and this deterioration is predictive of subclinical atherosclerosis and future cardiovascular events^[8]. Aortic strain and distensibility tend to be significantly lower, and the aortic stiffness index significantly higher, in untreated CD patients vs controls^[8,10]. CD patients are at increased risk for

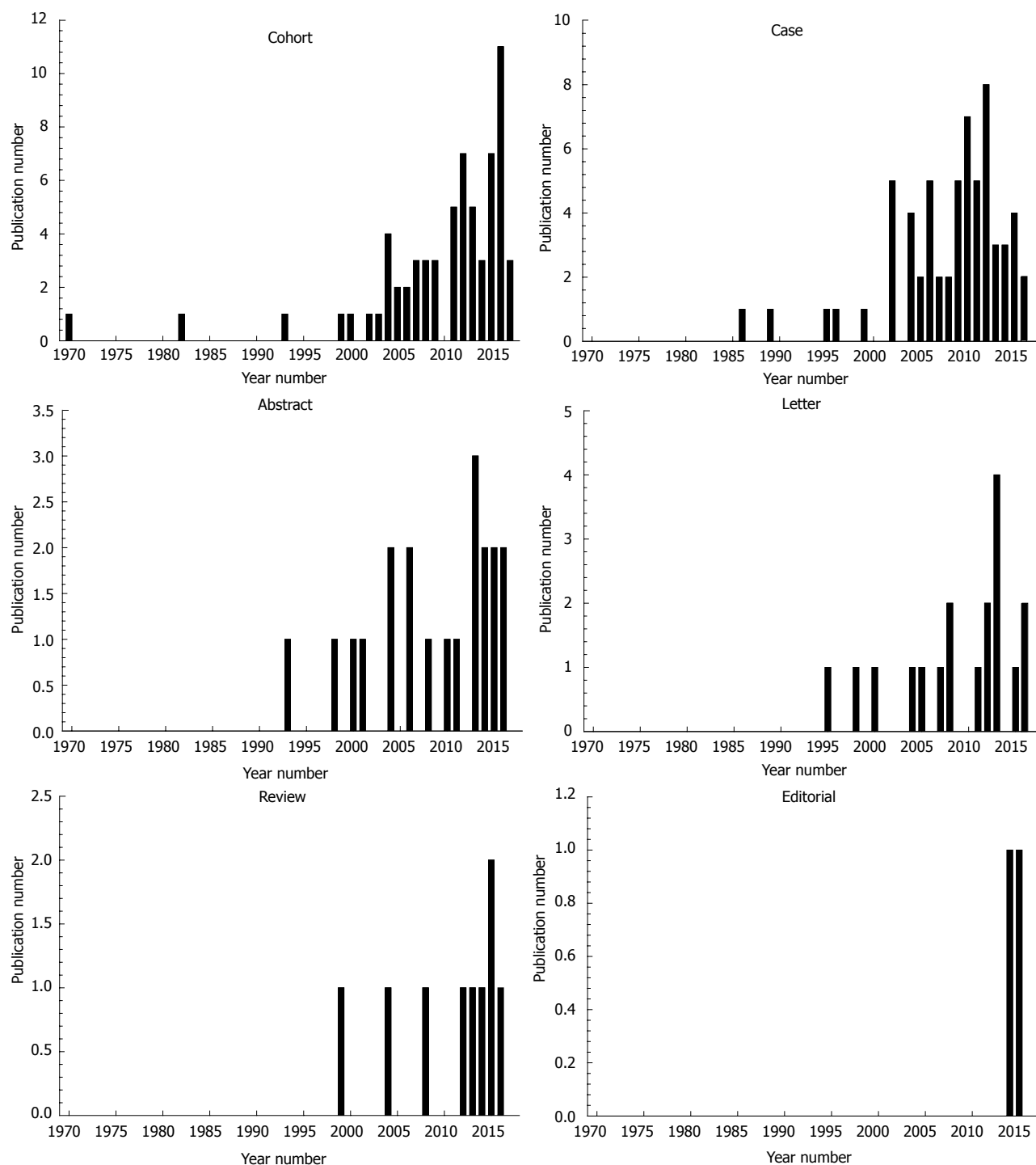


Figure 2 Published studies per year according to document type.

coronary artery disease^[9], which may have a genetic association^[11]. Occlusion of the brachiocephalic trunk and right and left common carotid artery has been noted in CD^[12]. In adult CD patients lacking cardiovascular risk factors, abnormal homocysteine, erythrocyte sedimentation rate, C-reactive protein, and insulin levels may, along with inflammation, be contributive to arterial stiffening^[9]. Spontaneous coronary artery dissections have been observed as a cause of acute myocardial infarction in CD patients^[3]. There is also some support

for an association between CD and cerebrovascular disease^[13]. Correlation has been shown between restoration of the small intestinal villous atrophy and normalization of vascular parameters in gluten-abstinent CD patients^[14]. Yet after onset of the GFD, the lack of a significant reduction in aortic elastic properties suggests that some risk of cardiovascular disease may persist^[10]. Type 1 diabetic patients with early presence of micro- or macrovascular complications should always be screened for CD^[15]. Type I diabetes mellitus and CD can coexist,

Table 3 Types of studies associated with each keyword

Keyword	Article	Review	Case	Letter	Abstract	Editorial	Total
Arterial function	6	1	2	2			11
Atherosclerosis	4		1	5	3		13
Angiogenesis	6				1		7
Thrombosis	4	2	15	5	1		27
Stroke	2	2	7		1		12
Hemorrhage			7	3			10
Haemodynamics	1			1	2		4
Vascular - other	2		3				5
Pericardial effusion	2		1		1		4
Myocarditis	3	1	1	1			6
Cardiomyopathy	8	1	21	0	2	1	33
Infarction	4			1			5
Electromechanical	6				1		7
Ischemic heart disease	6			3	1	1	11
Rhythm disturbances	3		1	1	3		8
Congenital heart defect	3		1				4
Heart - other	3		2		1		6
Cardiovascular risk	11	2		1	3		17
Total	74	9	62	23	20	2	190

Table 4 Characteristics of the published studies by keyword

Category	Topic	Studies ¹	Median year	Range
Vascular	Arterial function	11	2014	2011-2016
Vascular	Atherosclerosis	13	2013	2008-2016
Vascular	Angiogenesis	7	2009	1970-2013
Vascular	Thrombosis	27	2007	1995-2016
Vascular	Stroke	12	2008	2001-2017
Vascular	Hemorrhage	10	2007	1997-2012
Vascular	Haemodynamics	4	1998	1993-2005
Vascular	Other	5	2004	1993-2013
Heart	Pericardial effusion	4	2008	2000-2014
Heart	Myocarditis	6	2004	2002-2012
Heart	Cardiomyopathy	33	2010	1986-2016
Heart	Infarction	5	2009	2008-2015
Heart	Electromechanical	7	2014	2008-2016
Heart	Ischemic heart disease	11	2014	2004-2016
Heart	Rhythm disturbances	8	2014	1989-2016
Heart	Congenital heart defect	4	2014	1982-2016
Heart	Other	6	2012	2004-2016
Cardiovascular disease	Risk factors	17	2013	2007-2017

¹Studies: Total number of studies published on the topic. Studies could be used as references for more than one topic.

and there is evidence that microvascular complications are more severe in patients with both conditions^[16,17].

Vascular - atherosclerosis [# = 13, median year = 2013 (2008-2016)]

Atherosclerosis has been linked to myocardial infarction and ischemic stroke, with chronic inflammation being a likely pathogenic factor^[18]. Untreated adults with CD are at increased risk of early atherosclerosis, as suggested by the presence of chronic inflammation, vascular impairment, unfavorable biochemical patterns^[19-21],

and relative lack of the classical risk factors. Carotid intima-media thickness values are significantly higher in patients with coexisting diabetes and CD as compared to those patients with diabetes or CD alone^[16,22]. CD youth have also been associated with increased risk of developing early atherosclerosis^[19]. They are also more likely to have greater mean low density lipoprotein (LDL) cholesterol and thicker carotid intima media as compared with controls, and their endothelium-dependent dilatation is decreased, all of which negatively affect vascular function^[23,24]. The GFD enables a reduction in inflammatory parameters, oxidative stress, and insulin resistance, factors that when unchecked can lead to atherosclerosis^[10,25]. Gluten avoidance followed by restoration of the intestinal villi to normal function is likely to revert cardiovascular dysfunction in less than 1 years' time^[2,20,21,23,24]. Areas with improved markers on a GFD include the common carotid arteries for intima media thickness, and the humeral artery for endothelium-dependent dilatation^[26]. However, patients on the GFD often show weight gain and increase in triglyceride blood levels, which suggests a risk to atherogenicity^[27], although alterations of other risk factors do not necessarily support this supposition^[28]. CD patients should always be encouraged to choose a healthy GFD^[27].

Vascular - angiogenesis [# = 7, median year = 2009 (1970-2013)]

In untreated CD, the overall architecture of the small-bowel mucosal vasculature may be altered, leading to inhibition of angiogenesis^[29]. On the GFD, the vasculature normalizes as compared to healthy subjects, in parallel to mucosal recovery, and mucosal autoantibody deposits diminish in the small intestine^[29,30]. Autoantibody production in CD mainly targets against transglutaminase 2 (TG2)^[29]. These autoantibodies are found in untreated

CD patients' serum^[31], but also bound to extracellular TG2 below the epithelial basement membrane and around capillaries in the small intestinal mucosa, as well as in extra-intestinal organs. The autoantibodies can interfere with angiogenesis, including changes in transendothelial migration of lymphocytes^[29,32,33], which is probably influenced by common genetic variants in angiogenesis-related genes^[34]. *In vitro*, CD autoantibodies reduce endothelial branching, increase endothelial permeability to macromolecules and lymphocytes, and enhance lymphocyte adhesion to the endothelium^[29,35]. Ultrastructural alterations of the small blood vessels embedded in the subepithelial connective tissue of the jejunal mucosa are most severe in CD patients not on the GFD. Similar changes occur when gluten is administered to pediatric CD patients previously on a GFD, and are one of the earliest pathological changes seen in the biopsy material^[35].

Vascular - thrombosis [# = 27, median year = 2007 (1995-2016)]

Thrombotic events are increased in CD^[36], can be recurrent^[37], and may be present at multiple locations^[38] which are observable *via* Doppler ultrasonographic examination^[39]. Thrombophilia may result from hyperhomocysteinemia and deficiencies in protein S, folate, and vitamin B2^[40-42]. The thrombotic events in CD may also result from dehydration due to diarrhea^[43]. Cerebral venous sinus thrombosis can occur in CD patients^[40,44-46], even in absence of gastrointestinal symptoms^[45], but can resolve with symptomatic treatment^[40]. Venous thrombosis can be a sequela of undetected CD^[42,47-54], and may result in thromboembolic events^[48,55]. CD may be accompanied by portal vein thrombosis^[56,57], and mesenteric^[58] or splenic^[59] vein thrombosis may present in occult or subclinical celiac disease^[58]. There is an increased risk of developing venous thromboembolism from chronic inflammation and vitamin deficiency in CD^[44,60,61]. On a GFD, there is favorable evolution of young CD patients with thrombosis^[62]. CD should be considered in young patients with thrombosis, especially if the event occurs in an unusual location^[62].

Vascular - stroke [# = 12, median year = 2008 (2001-2017)]

Patients with CD have been found to be at an increased risk for stroke, which can persist after onset of the GFD^[63,64]. Stroke events can be recurrent^[65]. Cerebral infarction and transient hemiplegia may also present in untreated asymptomatic CD patients^[66]. CD should be considered as a possible etiology for stroke cases of unknown cause, particularly in youth, whether gastrointestinal manifestations are evident or not^[67]. The pathogenesis of stroke in CD youth may involve vitamin B12 deficiency^[68] and possibly hyperhomocysteinemia, which may be secondary to folic acid deficiency^[69], cerebral arterial vasculopathy, and antiphospholipid

syndrome, a secondary autoimmune disorder^[70-72]. Children with recurrent acute ischemic stroke should be screened for CD^[73]. Because CD is a potentially treatable cause of cerebral vasculopathy and stroke^[74], serology-specifically anti TTG antibodies should be included in the evaluation for cryptogenic stroke in childhood, even in the absence of typical gastrointestinal symptoms^[72].

Vascular - hemorrhage [# = 10, median year = 2007 (1997-2012)]

When unresponsive CD is treated with corticosteroids and immunosuppression therapy, it can be complicated by the presence of small intestinal lymphoma, and result in hemorrhage^[75,76]. During hemorrhage, coagulopathy can occur, which is attributable to vitamin K deficiency associated with malabsorption of multiple fat soluble vitamins in these patients^[75]. The immune response to CD, triggered by gluten, can lead to deposition of circulating immune complexes on the membrane of alveolar capillaries, resulting in pulmonary hemosiderosis^[77]. Lane-Hamilton syndrome refers to the co-occurrence of idiopathic pulmonary hemosiderosis and CD^[78]. Idiopathic pulmonary hemosiderosis is severe and potentially fatal, and is characterized by recurrent episodes of alveolar hemorrhage, hemoptysis, and anemia, and can share a common immune pathway with CD^[79]. Left untreated, it can lead to poor prognosis, with progression to pulmonary fibrosis and chronic respiratory limitation^[80]. In patients with diffuse alveolar hemorrhage, even in the absence of gastrointestinal symptoms, screening for CD should be done using anti-transglutaminase antibodies^[79,81]. If CD is found, the GFD helps control symptoms, enables a reduction of immunosuppressive treatment, and improves clinical course^[79]. Improvement of the co-occurrence of CD and pulmonary hemosiderosis over a period of months is found when patients are placed on the GFD^[82,83]. Thus patients with pulmonary hemosiderosis should always be screened for CD^[80,82]. Patients with hereditary hemorrhagic telangiectasia with unexplained iron malabsorption should also be screened for CD^[84].

Vascular - haemodynamics [# = 4, median year = 1998 (1993-2005)]

Alteration of blood flow is an important issue. The pathophysiological changes in the small bowel mucosa during the active phase of CD can induce haemodynamic changes^[85] including an abnormal splanchnic circulation^[86], and splenic vein obstruction may be present^[47]. The postprandial mesenteric blood flow can be significantly increased and delayed in time^[86]. A hyperdynamic mesenteric circulation and higher peak systolic velocity of the superior mesenteric artery is often manifested in untreated CD patients as compared with healthy controls and treated celiac patients^[85,87]. Treatment with the GFD can improve haemodynamics^[85,87].

Vascular - other [# = 5, median year = 2004 (1993-2013)]

Several other vascular maladies have been noted to occur in conjunction with CD. The combination of CD, epilepsy, and cerebral calcification is a rare condition known as CEC syndrome^[88]. Folate malabsorption is a suggested mechanism, because cerebral calcification can be seen in other conditions related to folate deficiency^[88]. Membranous obstruction of the inferior vena cava can also occur^[89]. In patients with hyperhomocysteinaemia and sub-clinical CD, endothelial dysfunction is associated with increased systemic vascular resistance that can lead to a reversible form of hypertension^[90]. CD adults tend to have a lower prevalence of hypertension and hypercholesterolaemia as compared with the general population^[91]. However in patients with hypertension, CD, and hyperhomocysteinaemia (*via* malabsorption of essential cofactors), CD treatment can improve blood pressure control^[90]. Covert hemoptysis may be responsible for disproportionately severe anemia in CD patients^[92].

Heart - pericardial effusion [# = 4, median year = 2008 (2000-2014)]

The heart itself can be greatly affected in CD patients. Echocardiography has been used to show that there is a higher incidence of pericardial effusion in CD^[93]. In adults, this phenomenon can be asymptomatic^[94]. The predisposing factors for pericardial effusion include vessel dysfunction in the presence of high antibody titer, selenium deficiency, and viral infection due to reduced immunological competence, in conjunction with a diminished ability to eliminate toxic free radicals^[93,95]. After onset of the GFD and with iron supplement, pericardial effusion, along with peripheral edema and fatigue, decreases^[94,96]. Presence of left ventricle dilation, suggesting an initial phase of heart damage, is reversible on the GFD^[96]. CD children may also have pericardial fluid, and show no difference compared to those lacking effusion with respect to ECG, chest X-ray, blood cell count, serum enzymes, serum protein, and iron levels^[95]. Pericardial effusion is reversible in children when they are treated with a GFD^[95,96]. Thus pediatric cardiologists should be alerted to the possibility that mild left ventricular enlargement can be caused by CD^[96].

Heart - Myocarditis [# = 6, median year = 2004 (2002-2012)]

Autoimmune myocarditis may be a complication of CD^[97]. Biopsy-proven granulocytic myocarditis of unknown etiology can be found in the setting of silent CD^[98]. Progressive heart failure may accompany viral myocarditis in untreated CD; patient condition can improve following standard heart failure treatment and GFD^[99]. A strong fluorescence around heart muscle fibers has been noted in untreated CD patients but not in patients on the diet or in controls^[100]. This suggests that an autoimmune process toward antigenic components of the myocardium can occur in untreated

CD, and lead to cardiac tissue injury, resulting in myocarditis^[101]. In these patients, immunosuppression and GFD are often effective therapeutic options^[101]. It is thus highly important to screen for CD in patients with these conditions to avoid progression and clinical deterioration^[102]. It has been found that the CD prevalence in children with myocarditis is greater than in children without myocarditis^[102], who should therefore also receive CD screening.

Heart - cardiomyopathy [# = 33, median year = 2010 (1986-2016)]

Cardiomyopathy associated with CD is a serious and potentially lethal condition which requires a multidisciplinary approach involving both a gastroenterologist and a cardiologist^[103-106]. There is a higher prevalence of CD in patients with dilated cardiomyopathy^[107-109], idiopathic cardiomyopathy^[110-113] and ischaemic or valvular cardiomyopathy^[110]. There is also a higher prevalence of CD in the relatives of patients with sporadic and inherited dilated cardiomyopathy^[114]. Severely dilated left ventricle, concomitant left ventricular dysfunction, very low ejection fraction, pulmonary hemosiderosis, heart block, and/or heart failure have been reported in cardiomyopathy patients with CD^[112,115-120]. Severe progressive dilated cardiomyopathy, requiring heart transplantation, can occur^[121]. Dilated cardiomyopathy in CD may be accompanied by congestive heart failure and is also becoming increasingly recognized in the pediatric population^[122,123]. These children may also present with acute onset congestive heart failure, as well as severe left ventricular systolic dysfunction^[123]. Upper limb venous thrombosis and recurrent haemoptysis secondary to pulmonary haemosiderosis may be present^[123]. Cirrhotic cardiomyopathy without gastrointestinal symptoms has also been found in pediatric patients^[124].

Although a serious condition, the precise cause-and-effect relationship between CD and cardiomyopathy when they occur in tandem is currently unknown^[125]. Dilated cardiomyopathy may evolve due to carnitine deficiency^[126,127], which is related to CD, but may also develop after onset of the GFD, particularly in patients lacking carnitine supplementation^[126]. Idiopathic dilated cardiomyopathy may have an autoimmune mechanism^[110,128]. The tTG-positive serology in relatives with echocardiographic abnormalities suggests that immune-mediated mechanisms are at work in subsets of these patients and their families^[106]. In individuals with idiopathic congestive cardiomyopathy and CD, ultrastructural and electrophoretic examination of myocardial samples shows a selective loss of actin, and electron microscopy reveals characteristic alterations of enterocyte microvilli^[129]. Hence there can be an involvement of the microfilament system in both the myocardial sarcomeres and the enterocytes of these patients^[129]. Ischemic cardiomyopathy can occur due to an accelerated atherosclerosis when chronic inflammation is present in CD^[130].

Compliance with a GFD is mandatory if patients are

to avoid progression of their cardiomyopathy^[105,131]. The GFD has been shown to have a beneficial effect on cardiac performance in CD patients with dilated cardiomyopathy^[132]. After start of the GFD, abnormal left ventricular dimensions, and diminished cardiac function, including decreased ejection fraction, can improve markedly and may even be completely reversible^[103,108,118,128,133]. After two years on a GFD, patients presenting with dilated cardiomyopathy associated with CD show progressive increase in mean serum carnitine levels as compared to values observed prior to the diet^[127]. Children with CD and dilated cardiomyopathy also have improved cardiac function once adherent to the GFD^[109]. In CD patients on the GFD, there is no association with later onset of myocarditis, cardiomyopathy or pericarditis^[134].

Screening for CD in patients with dilated cardiomyopathy, pulmonary haemosiderosis, and iron deficiency anemia in the absence of known etiology is advisable regardless of the intestinal symptoms^[105,108,116,123,133]. Serologic tests for IgA-EmA and tissue transglutaminase antibodies should be used to screen for CD^[106]. Comorbidities including iron-deficiency anemia in patients with dilated cardiomyopathy should arouse suspicion of CD^[117]. All patients diagnosed with cardiomyopathy and CD should be offered an endomyocardial biopsy for better histological and diagnostic definition^[128]. It is beneficial to assess CD in children with dilated cardiomyopathy in the absence of known etiologies^[104,135].

Heart - infarction [# = 5, median year = 2009 (2008-2015)]

Acute myocardial infarction with ST-elevation and spontaneous coronary artery dissection can occur in young patients with CD^[3,136]. However, chronic hypocalcemia in untreated CD patients due to poor absorption of minerals can result in electrocardiographic changes that mimic acute myocardial infarction^[120]. In CD, there is a higher all-cause mortality one year post-myocardial infarction as compared with the general population^[20]. Mesenteric infarction has also occurred as a consequence of CD, and clinicians should be aware of this possibility^[137].

Heart - electromechanical functioning [# = 7, median year = 2014 (2008-2016)]

Measurement of electromechanical parameters is beneficial to determine the degree of cardiac involvement in CD^[138]. Atrial conduction delays are significantly higher in untreated CD as compared with healthy individuals, and may lead to atrial fibrillation^[139]. Measurement of atrial electromechanical delay parameters might therefore be useful to predict atrial fibrillation risk^[139]. Statistically significant differences in left ventricular function as assessed by echocardiography imaging are found in CD patients vs controls^[140]. Patients with CD can have impaired diastolic and systolic function as measured by tissue Doppler echocardiography^[141]. Mitral valve prolapse^[142] and subclinical myocardial dysfunction of

both ventricles^[143] can be present in both the pediatric and adult CD population. In children, significantly lower contractility indices and higher left ventricular dimensions are evident as compared with controls^[144]. On the GFD, valve regurgitations resolve, and echocardiographic parameters significantly improve^[144].

Heart - ischemic heart disease [# = 11, median year = 2014 (2004-2016)]

There is an increased risk of ischemic heart disease and higher cardiovascular mortality in CD^[145,146] despite the lack of traditional risk factors^[26,147] including blood pressure, body mass index, serum cholesterol, lipids, exercise, and smoking^[4,148]. First-degree relatives of CD patients are also at an increased risk of ischemic heart disease, but the excess risk is slight^[149]. CD and ischemic heart disease may share a common underlying link, rather than a cause-and-effect relationship^[18,150]. The underlying association between CD and ischemic heart disease may be chronic inflammation, a major risk factor in the general population; however, potential confounders may also be involved^[18,146,148]. After onset of the GFD, persistent villous atrophy detected during follow-up biopsy was not associated with increased risk of ischemic heart disease^[151,152].

Rhythm disturbances [# = 8, median year = 2014 (1989-2016)]

Compared to controls, untreated CD patients have increased P-wave dispersion and higher interatrial, intra-left atrial, and intra-right atrial conduction delay^[153]. Tp-e interval, Tp-e/QT and Tp-e/QTc ratios are also increased in CD^[154]. There is a higher prevalence of atrial fibrillation among CD patients^[153,155]. Atrial fibrillation, when it occurs, is associated with an increased risk of ischaemic stroke and heart failure^[156]. The chronic inflammation that can occur in untreated CD is a recognized risk factor for atrial fibrillation^[155,156]. CD patients have slower atrial electrical conduction, which may also increase the risk of atrial fibrillation^[153]. However, persistent villous atrophy on follow-up biopsy was not associated with any increased risk of atrial fibrillation^[151,152]. It has been reported that CD patients with pulmonary hemosiderosis can develop infranodal heart block, necessitating implantation of a pacemaker^[77,157]. These patients may lack digestive manifestations but have iron deficiency and vitamin deficiency anemia^[77]. Rhythm alterations in CD can thus result from other pathogenic mechanisms including electrolyte disturbances caused by malabsorption, which can normalize on the GFD^[77]. Patients with rhythm disturbances and chronic anemia of unclear origin should therefore be tested for CD^[77].

Heart - congenital heart defect [# = 4, median year = 2014 (1982-2016)]

CD patients are likely to more commonly have atrial septal defect as compared to controls^[158]. Screening

for CD in children with congenital heart defect is recommended, since serum TTG IgA levels are significantly higher in patients with congenital heart defect vs control children^[159]. Down syndrome patients with congenital heart defect have higher CD prevalence as compared to patients without congenital heart defect, and CD prevalence in Down syndrome patients is higher than in controls^[160]. In children with congenital heart disease and CD, growth improves on a GFD^[161].

Heart - other [# = 6, median year = 2012 (2004-2016)]

Chronic hypocalcemia, which may occur in untreated CD due to malabsorption, has been associated with reversible cardiac dysfunction^[120]. Untreated CD children tend to show an imbalance of cardiac sympathetic and parasympathetic activity due to enhanced sympathetic tone^[162]. This imbalance is still detected after a six months period of GFD^[162]. This suggests the presence of a subclinical autonomic nervous system dysfunction^[162]. There is a higher prevalence of CD in patients with Postural Orthostatic Tachycardia Syndrome (POTS)^[163], thus these patients should also be screened for CD^[164]. Left ventricular hypertrabeculation/noncompaction may be associated with CD^[165]. Subclinical systolic dysfunction of the left ventricle may be present in CD children^[166].

Cardiovascular disease risk factors [# = 17, median year = 2013 (2007-2017)]

Cardiovascular disease (CVD) as a whole has many etiologies and is the leading cause of death in developed countries^[167,168]. There is a modestly increased risk of CVD in CD patients^[63]. Both male and female CD patients may have higher estimated risk for CVD as compared to controls^[169,170]. However, CVD risk factors conferred by CD have not been well-defined^[171]. This has led to conflicting evidence as to whether CD patients actually have increased baseline risk^[172]. CD patients are susceptible to increased platelet activation and increased mean platelet volume and RDW values, factors that contribute to increased risk^[173,174]. Using the Framingham Heart Study (FRS) 10-year general CVD risk score, lower values were found among CD patients as compared with controls, which may be due to a lesser body mass index and reduced tobacco use among CD patients^[171]. Risk factors other than those measured by the FRS may be observed as increased risk of CVD in CD patients^[171]. There can also be a positive association between CD and CVD risk due to ascertainment bias^[175]. In CD children, risk factors can be frequently observed as compared with healthy subjects^[18]. Overall, certain CVD risk factors have been found to be higher in CD youth as compared with the general population, although neither blood pressure nor overweight and obesity rates were increased^[176]. Youth with type 1 diabetes and CD had lower high density lipoprotein (HDL) cholesterol, increasing CVD risk, as compared with non CD patients^[177].

The lack of a uniform set of risk factors can influence whether CVD risk is affected by a GFD^[172]. In actuality, both risk and protective factors for CVD are likely to be present in CD, at baseline and also on a GFD^[172]. Modifiable risk factors for CVD can include body mass index and cholesterol, which have been shown to increase on the GFD^[168]. In CD individuals with type 1 diabetes on a GFD, improvement in HDL-cholesterol, and a lower resting heart rate, has been demonstrated as compared with those CD patients without diabetes^[178]. On a GFD, the lipid profile of CD patients can also improve^[17]. At one year on a GFD, waist circumference may increase, but without significant rise in total or LDL cholesterol^[173,174]. The GFD should therefore ideally go beyond gluten exclusion and include body weight control and high quality nutrients^[172]. A relatively high proportion of CD children on the GFD had one or more CVD risk factors^[179]. The most common CVD risk factors are high fasting triglycerides, elevated blood pressure, and high LDL cholesterol concentrations^[179]. Insulin resistance is also found, underscoring the need for CVD screening and dietary counseling targeting the pediatric CD population^[179]. Screening for CD and monitoring of HDL cholesterol is recommended in youth with type 1 diabetes^[177]. CVD risk factors also include metabolic disorders caused by malabsorption in pediatric CD patients^[180]. Hence timely correction of water and electrolyte imbalance, and administration of cardiometabolic therapy, is necessary^[180].

CONCLUSION

Published studies pertaining to the connection between cardiovascular conditions and CD began in the late 1960's, consisting of a few studies each year, and was followed by a substantial increase beginning about the year 2000. Many of the published studies are either articles (including cohort and case control studies) or case studies consisting of one to three patients. Often, as might be expected, a number of case studies appeared in the literature prior to the cohort studies. Based on the evidence presented in these papers, it is apparent that cardiovascular involvement in CD is a real phenomenon and that there are many manifestations, owing to the multifaceted, systemic physiological changes that can occur in CD. A number of the cardiovascular issues that can occur in untreated CD patients, will resolve on a GFD, often in conjunction with healing of the small intestinal villi. Cardiomyopathy is the most frequently documented cardiovascular condition observed in conjunction with CD, and seems to mostly or completely resolve with appropriate treatment, including a GFD. However, if CD is left unrecognized until a late stage, damage done to the heart may not be entirely reversible. Similarly, to the present time there has been substantial documentation of a number of other cardiovascular conditions found in conjunction with untreated CD including

thrombosis and thromboembolism, ischemic heart disease, stroke, and arrhythmia. There has also been significant investigation of CD and risk of cardiovascular disease. On this topic, a current problem is that there is no uniform set of cardiovascular risk factors used for analysis. Future studies should settle the question of how to best treat these co-occurring conditions, and to determine if other cardiovascular manifestations of CD are common phenomena.

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Is there evidence for statins in the treatment of aortic valve stenosis?

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Abstract

Research revealed that the pathogenesis of aortic stenosis (AS) not merely comprises of a mechanical wear and tear process yet that active biological processes, similar to

those of coronary artery disease are involved, a promising role for statins in disease-modifying therapy was suggested. However, recently, many prospective studies could not observe decreased progression nor regression of the disease. Here, we review the current knowledge on the pathomechanisms of AS and its similarities and differences with atherosclerosis. Moreover, we discuss whether there is still a place for statins in the treatment of particular AS patient subgroups.

Key words: Aortic stenosis; Statins; HMG-CoA enzyme inhibitor; Coronary artery stenosis; Aortic valve surgery

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Core tip: Aortic stenosis is a age-dependent and growing disease. As there are several similarities with atherosclerotic disease of other regions there are growing research on underlying pathophysiology. The treatment benefit of classic atherosclerosis treatment is evaluated in case of aortic valve stenosis.

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INTRODUCTION

Aortic stenosis (AS) is the most common heart valve disease in Western countries. It affects 12.4% of the population over the age of 75 years^[1] with a male predominance of 80% in symptomatic AS^[2]. AS is usually characterized by an asymptomatic latent period of several years or even decades before patients suffer from discomforts. However, once patients with severe AS display symptoms (typically

syncope, angina and/or dyspnoea), the prognosis is poor with a 2-year and 5-year survival rate of 50% and 20%, respectively; hence valve replacement surgery is usually mandated^[3]. Since the elderly population in Western countries is expected to double by 2050, it is imperative to define early diagnostic and treatment strategies. Even though AS or the fibrous thickening and calcification of the valves is a widespread disease, its underlying molecular mechanisms are still unknown^[4]. Traditionally, it was accepted that AS is caused by the progression of calcium deposition continued to aortic valvular leaflets. However, research demonstrating the involvement of active cellular processes over the past 15 years^[5]. Genetic polymorphism seems to influence the degree of aortic valve sclerosis^[6], with a focus on chronic inflammatory processes. Moreover, it has become clear that the development of AS shows many similarities with atherosclerosis including infiltration and retention of lipoproteins, lipids, T-lymphocyte and other inflammatory cells, as well as osteoblastic activation^[7-9]. Accordingly, numerous studies demonstrated a strong association to coronary artery disease (CAD) and many of its risk factors, including hypercholesterolemia^[10,11]. This opened the field to develop effective disease-modifying strategies, which would halt or even regress the disease, thus avoiding the need of surgical or interventional replacement. At first, statins seem to be the most obvious medical treatment choice since its use is well-established for the primary and secondary prevention of CAD^[12]. Moreover, statins have been shown to exert pleiotropic effects beyond their cholesterol-lowering effect, such as anti-oxidation, plaques stabilization and reduction of vascular inflammatory processes^[13,14]. Numerous retrospective observational studies showed a delay in AS progression when statins were administered concomitantly which encouraged the use of statins for treatment of AS^[15-19]. However, 3 recent large-scale prospective randomized clinical trials investigating the effects of intense lipid-lowering therapy with statins showed no effect on neither progression, nor regression of AS. Meanwhile, new insights are emerging, demonstrating distinct differences in (molecular) pathology between CAD and AS. Here, we review what is known today about the pathogenesis of AS and the potential influence of statin therapy in AS patients, with a distinction between degenerative or calcific AS, congenital AS, AS with coronary heart disease as comorbidity, and, treatment before and after aortic valve surgery.

PATHOMECHANISMS OF DEGENERATIVE OR CALCIFIC AS AND CAD: SIMILARITIES AND DIFFERENCES

Since it became clear that AS is not merely the result of mechanical stress and ageing, but rather an active biological processes involving inflammatory contributing

to the disease; pharmacological treatment possibilities were completely opposed to valve replacement surgery inevitable at the time when AS has reached a severe symptomatic status. What has been revealed of the current knowledge of the pathogenesis of AS so far, revealed many similarities with CAD. Hence, it was obvious to turn to statins for the treatment of AS since they have proven efficacy for the primary and secondary prevention of CAD. Nevertheless, it is shown that, besides lipid-lowering, statins display pleiotropic effects such as anti-inflammatory and antioxidant effects as well as plaque-stabilization and improvement of endothelium dysfunction^[20] (Figure 1). The potential use of statins was initially encouraged by positive results from numerous retrospective studies. Yet recently, three prospective randomized studies showed neither regression, nor reduction in progression of AS: SEAS (Simvastatin and Ezetimibe in Aortic Stenosis), SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression) and ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin)^[21-23]. All three trials demonstrated that extensive lipid-lowering induced by statins failed to correlate with neither improvement of aortic-jet velocity of the valve, nor with regression of valvular calcification. Such disappointing results were surprising because of the many well recognized similarities between CAD and AS in terms of pathogenesis. Moreover, statin use has become an established principle for CAD. Furthermore, similar risk factors have been identified for both diseases such as age, sex (male gender), dyslipidaemia, hypertension, smoking, diabetes and renal dysfunction^[24,25]. Aortic valve stenosis can be characterized an 'early lesion', which are similar to those of atherosclerotic plaques in vessels^[8] and both CAD and AS are characterized by infiltration and accumulation of (oxidized) low-density lipoproteins (LDL) and T-lymphocytes, thus filling tissue inflammation and the release of pro-inflammatory cytokines such as tumour necrosis factor (TNF)- α and interleukin (IL)-1 α which in turn induce cell proliferation^[7,9,26]. Calcification and osteogenesis, mediated by inflammation and processes involving metalloproteinases, have been identified as players in the pathogenesis of AS^[27-29]. Finally, neo-angiogenesis contributes to AS development^[30,31] and is responsible for reduced concentrations of the anti-angiogenesis protein chondromodulin-1 in damaged aortic valve tissue^[32]. The resulting cell apoptosis, extracellular matrix formation and consequent thickening and calcification of the cusps, decreases aortic valve mobility and orifice areas, ultimately leading to an increased pressure gradient^[33]. Nevertheless, there are some fundamental differences in the underlying molecular mechanisms with an early inflammation affecting fibroblasts in AS as opposed to late onset of inflammation in smooth muscle cells in CAD. Yet, plaque instability is not the leading clinical problem with AS; however clearly the main cause of symptoms with CAD^[34]. It is important to note that

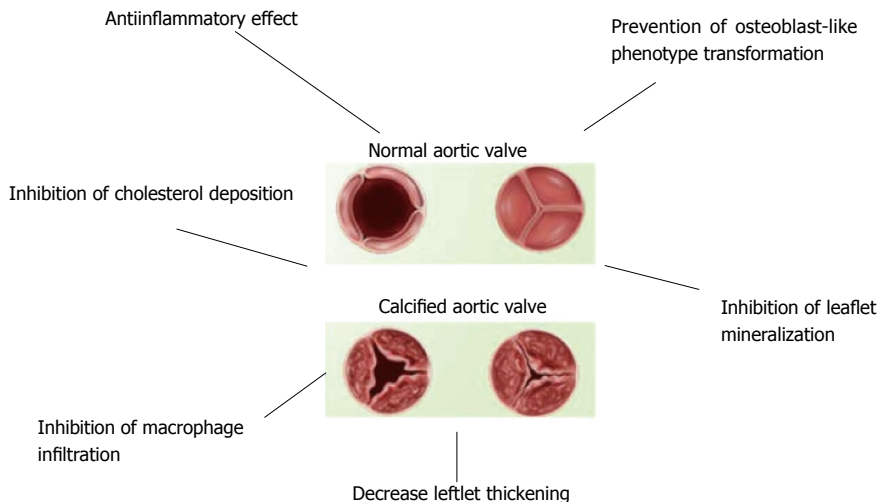


Figure 1 Schematic overview of statin effects on aortic valve calcification.

those retrospective studies on the effect of statins in AS included patients already exposed to statins prescribed for primary or secondary prevention of CAD. Moreover, study patients had only mild to moderate AS as severe AS was excluded. Based on sub-analyses of the 3 RCT's, several research groups support the lipid hypothesis as a common denominator of both diseases, with similarities between atherosclerosis and AS seen in initial stages of AS. Later on, disease progression is mostly determined by plasticity and structure of the leaflets, and by mechanical stress^[35,36]. Yet, results of a recent meta-analysis challenged suggested role of statins to prevent the onset of AS in non-symptomatic patients^[37]. They pooled high risk patients without known AS from 3 large scale RCT's who evaluated the effect of high (80 mg) and normal (10 mg) daily doses of atorvastatin and found no significant differences between placebo, low or high atorvastatin with regards to the onset of AS. Furthermore, across the board any subtle correlation between hyperlipidaemia and AS progression^[15,17] turned out to be inconsistent^[18,19].

Effect of statins on AS in patients with CAD

As much as 40% of patients undergoing aortic valve replacement surgery suffers from atherosclerosis as well. Moreover, AS progresses faster in older patients with CAD^[2]. There is evidence of beneficial effects of statins in presence of CAD^[38]. Dyslipidaemia is an independent predictor of AS progression and adequate lipid-lowering by statin use in patients with CAD has beneficial effects on valve integrity^[39]. Yet, a quantitative relationship between lipid-lowering and changes in AS progression has not been found. It is worth mentioning that most studies investigated patients with intermediate or advanced AS which appears difficult to modify by drugs; however, a potential effect in early AS could still be debated^[40]. Another point to address is patient selection bias, especially in the SEAS trial that excluded patients

with diabetes or CAD. Even though no correlation between statin use and beneficial effects on AS have been shown, it is highly likely that patients with AS and relevant comorbidities such as atherosclerosis, which is a common clinical scenario, may be positively affected^[41,42]. Indeed, statins would mitigate AS progression only when hyperlipidaemia is present^[43] but more profound research is needed. Current guidelines suggest offering patients with comorbidities such as CAD, diabetes or hyperlipidaemia statins. Conversely, untreated metabolic syndrome in patients with AS is related to faster stenosis progression and worse prognosis^[44]. These observations were more pronounced in younger patients (< 57 years of age). Interestingly, however, statins in younger patients with metabolic syndrome and AS turned out to be disadvantageous with AS progression and lower insulin resistance supporting the notion that lipophilic statins may actually induce diabetes type II^[45,46]; this effect is even more pronounced when patients suffer from metabolic syndrome as well^[47]. This effect was not seen in older patients, suggesting that the pathophysiological mechanisms of AS progression may be related to the patient's age^[44].

CONGENITAL AORTIC STENOSIS

Congenital defects resulting in AS include partially fused leaflets, thickened leaflets, narrowing of the supra- or subvalvular area, and, most frequently, bicuspidity. A bicuspid aortic valve is the result of the fusion of two of the three leaflets during the developmental phase and is with an incidence of almost 2% the most common congenital cardiac malformation^[48]. The abnormal structure of the bicuspid aortic valve results in excess stress onto leaflets, resulting in valvular thickening, calcification, and increased rigidity and restricted aortic orifice. For that reason, AS is the most frequent complication of bicuspid aortic valve. While randomized prospective

trials mainly included older AS patients, the PROCAS (Progression of Stenosis in Adult Patients with Congenital Aortic Stenosis) trial was designed to evaluate the effect of statins on the progression of stenosis in young asymptomatic adults (aged between 18 and 45) with congenital AS. Not surprising, the investigators did not find any benefit from extensive lipid-lowering by 10 mg rosuvastatin, independent of the degree of valve calcification^[49]. These findings are in line with those of the bicuspid valve patients subgroup of the ASTRONOMER trial^[23].

STATIN THERAPY AND AORTIC VALVE SURGERY

Because of their anti-ischemic and anti-inflammatory effects and protection of the endothelium statins have been suggested to reduce atrial fibrillation after aortic valve surgery, yet with conflicting^[50,51]. Some beneficial effects of perioperative statin therapy on mortality, stroke, renal insufficiency, length of ICU and hospital stay were found^[52,53] however leading to the conclusion that preoperative statin use is justified in case of coronary artery bypass grafting (CABG). Indeed, advantageous effects on the above-mentioned endpoints have been demonstrated in only CABG patients and not in others^[54-56]. Conversely, just to add to the confusion statin were also reported to delay restenosis after balloon aortic valvuloplasty or bioprosthetic valve replacement^[57-59], but findings were not^[60]. With pre- and postoperative statin therapy in patients undergoing aortic valve replacement an increased long-term survival was found with biological valve replacement but not with mitral valve repair or mechanical valve replacement^[61]. Finally, a retrospective study of bicuspid aortic valve patients undergoing surgery showed a significant decrease in ascending aortic dilatation when exposed to statins preoperatively^[62]. Clearly, more clinical data are required to justify perioperative use of statin therapy.

FUTURE CONSIDERATIONS

Future research in this context needs to focus both, elucidating the molecular pathways involved in the pathogenesis of AS and developing potential pharmacological treatment strategies. In that regard, it is of interest to determine both vascular and valvular aspects and when they occur during the evolution of AS. As such, different treatment approaches might apply for distinct stages of the disease. In addition, defining predisposing genetic deviations may help define preventative and curative approaches to slow disease progression. Additionally, in the quest for new pharmacological agents to treat AS, low-cost accurate animal model are missing; only ageing swine can develop AS^[34]. At present, there is no evidence that statins halt the progression or induce the

regression of AS. The notion that their administration is harmless and devoid any side effects is untrue as we know adverse effects of statins in asymptomatic AS patients without concomitant diseases may in fact induce new risk factors (diabetes mellitus, aortic valve calcification)^[44,63]. In conclusion, the general consensus to date is that treatment with statins is not recommended in patients with valvular aortic stenosis and in absence of standard indications to lipid-lowering treatment.

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Basic Study

Interleukin-19 is cardioprotective in dominant negative cyclic adenosine monophosphate response-element binding protein-mediated heart failure in a sex-specific manner

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Abstract

AIM

To investigate the role of interleukin-19 (IL-19) in a murine model of female-dominant heart failure (HF).

METHODS

Expression of one copy of a phosphorylation-deficient cyclic adenosine monophosphate response-element binding protein (dnCREB) causes HF, with accelerated morbidity and mortality in female mice compared to males. We assessed expression of IL-19, its receptor isoforms IL-20R α/β , and downstream IL-19 signaling in this model of female-dominant HF. To test the hypothesis that IL-19 is cardioprotective in dnCREB-mediated HF, we generated a novel double transgenic (DTG) mouse of dnCREB and IL-19 knockout and assessed cardiac morbidity by echocardiography and survival of male and female mice.

RESULTS

IL-19 is expressed in the murine heart with decreased expression in dnCREB female compared to male mice. Further, the relative expression of the two IL-19 receptor isoforms manifests differently in the heart by sex and by disease. Male DTG mice had accelerated mortality and cardiac morbidity compared to dnCREB males, while female DTG mice showed no additional detriment, supporting the hypothesis that IL-19 is cardioprotective in this model.

CONCLUSION

Together, these data suggest IL-19 is an important cytokine mediating sex-specific cardiac (dys) function. Ongoing investigations will elucidate the mechanism(s) of sex-specific IL-19 mediated cardiac remodeling.

Key words: Cardiac dysfunction; Sex differences; Heart failure; Interleukin-19

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Core tip: Heart failure (HF) is a sexually dimorphic disease. In a female-dominant model of HF, the dominant negative cyclic AMP response-element binding protein (dnCREB) mouse, female mice show accelerated cardiac morbidity and mortality alongside downregulated interleukin-19 (IL-19) expression, while male mice maintain IL-19 expression and are protected against cardiac dysfunction. We generated a novel double transgenic mouse with dnCREB and IL-19 knockout to test the hypothesis that IL-19 is cardioprotective. We show accelerated cardiac morbidity only in male mice, supporting the hypothesis that IL-19 is a sex-specific cardioprotective cytokine.

Bruns DR, Ghincea AR, Ghincea CV, Azuma YT, Watson PA, Autieri MV, Walker LA. Interleukin-19 is cardioprotective in dominant negative cyclic adenosine monophosphate response-element binding protein-mediated heart failure in a sex-specific manner. *World J Cardiol* 2017; 9(8): 673-684 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/673.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.673>

INTRODUCTION

Heart failure (HF) is the leading cause of mortality within the United States, affecting more than 5 million Americans^[1]. HF is frequently perceived as a disease with poorer prognosis in male patients, perhaps since women are protected against cardiovascular disease premenopausally. However, many large-scale epidemiological studies do not support this conclusion. Sexually divergent manifestation of HF is observed regarding etiological factors, in response to a variety of HF therapies, and in presentation of HF and its comorbidities. Although the prevalence of HF is lower in women compared to men, treatment and survival outcomes for female patients are poorer with females having disproportionately higher morbidity and mortality^[1]. Women are more likely to be symptomatic and functionally limited^[2], experience less improvement following hospitalization^[3], and show higher level of disability at similar levels of left ventricular (LV) dysfunction with worse quality of life^[4] than male counter-parts. Together, the sex differences in HF highlight the necessity to understand female disease to close the gap in treatment and prognosis.

The deleterious effects of inflammatory cytokines in the context of HF are well documented as elevated circulating levels of cytokines predict adverse outcomes in patients with HF^[5]. Inflammatory cytokines directly affect cardiomyocyte contractility^[6], as well as influence LV remodeling and hypertrophy. Few studies, however, have examined sex-specific differences in cytokine expression, though sparse data indicate inflammatory profiles may be sexually dimorphic^[7]. Interleukin-19 (IL-19) is a member of the IL-10 subfamily of interleukins. IL-19 signals through an IL-20 receptor heterodimer IL-20R α and β to activate cytoplasmic tyrosine kinases of the Janus family signal transducer activator of transcription (JAK-STAT)^[8]. Differential relative expression of IL-20R subunits has been reported in different tissue types^[9] and is suggested as a potential mechanism of differential downstream IL-19 signaling, though this hypothesis has not yet been tested in the heart. While initially thought to be restricted to immune cells, IL-19 expression has since been observed in a wide variety of tissue types. IL-19 exerts both proinflammatory and anti-inflammatory properties, depending on tissue and disease specific factors^[10]. Previous work has demonstrated anti-inflammatory properties of IL-19 in endothelial and vascular smooth muscle cells^[8], but its role in the heart remains unknown.

Here, we investigated the expression of IL-19 and its receptor complex in a female dominant model of HF. Cardiac-specific expression of a dominant negative cyclic AMP response element-binding protein (dnCREB) results in dilated cardiomyopathy with accelerated mortality in female mice^[11]. In this model, the transcription factor CREB is rendered phosphorylation inactive *via* mutation of a critical Ser residue located

in the kinase-inducible domain the protein^[12]. In the unphosphorylated state, CREB can bind to DNA but cannot activate transcription, thus rendering the transcription factor inactive. This single nucleotide mutation results in significant cardiac dysfunction and accelerated morbidity and mortality in female mice compared to males. In comparison to male dnCREB mice, female dnCREB have significantly worse LV systolic function, higher heart rate, and diminished cardiac output, resulting in overall greater cardiac morbidity compared to male mice with the same genetic mutation^[11]. This exaggerated pathology in female dnCREB is particularly interesting, as the majority of HF models involving genetically manipulated mice demonstrate more profound morbidity in the male sex^[13]. In addition to this novel sexual divergence, the role of CREB in cardiac dysfunction is important, as CREB is functionally lost in rodent models of HF^[14] and loss of CREB-regulated genes is observed early in the failing human heart^[15]. Here, we show for the first time that IL-19 is expressed in the rodent heart, and is expressed in a sexually dimorphic manner in HF. Further, we demonstrate dysregulated downstream IL-19 signaling in female-dominant HF and suggest that IL-19 is cardioprotective in this model.

MATERIALS AND METHODS

Animals

The mouse model used in this study was a heterozygous, phosphorylation-deficient (Ser¹³³ to Ala¹³³) mutant CREB (dnCREB) transgenic mouse^[16] and non-transgenic (control, Con) littermates. dnCREB mice begin showing signs of contractile dysfunction at eight weeks of age. By 12 wk, female mice display significant mortality compared to males^[11]. Homozygous IL-19 knockout (IL-19 KO) mice were generated as previously described^[17] and show no overt signs of cardiac dysfunction or early morbidity and mortality. To have dnCREB and IL-19 KO mice on the same background, dnCREB mice were back-bred onto the C57 background for a minimum of 6 lineage passages. Male dnCREB mice were then crossed with female IL-19 KO to create heterozygous IL-19 KO. Male dnCREB IL-19 heterozygous mice from this F1 generation were then crossed with IL-19 KO female mice to create homozygous IL-19 KO and heterozygous dnCREB double transgenic male and female mice (DTG). Mice were housed at 4 per cage after weaning. Cages were inspected daily, and date of death noted for those mice found dead. Experiments were conducted in accordance with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals", and were approved by the Institutional Animal Care and Use Committee at the University of Colorado-Denver.

Echocardiography

Cardiac function was assessed by two-dimensional transthoracic echocardiography using a VisualSonics

Vevo 770 high-resolution ultrasound imager equipped with a 35-MHz transducer. Mice were lightly sedated with isoflurane and body temperature was maintained at 37 °C. Parasternal long- and short-axis B-mode videos and M-modes images (at the level of the midpapillary short axis) were routinely acquired. LV wall thicknesses and inner dimensions at diastole and systole were measured from the parasternal short-axis M-mode images.

Isolation of primary ventricular cardiac myocytes and fibroblasts

Cardiomyocytes were isolated from C57BL/6 male and female mice (approximately 14 wk of age) by enzymatic dissociation of the whole heart on a Langendorff apparatus as previously described^[18]. Briefly, hearts were rapidly removed and rinsed in a control buffer (133.5 mmol/L NaCl, 4mmol/L KCl, 1.2 mmol/L NaH₂PO₄, 10 mmol/L HEPES, 1.2 mmol/L MgSO₄, and 1% bovine serum albumin) to remove blood, weighed and mounted on a Langendorff apparatus. The isolated heart was then perfused at 37 °C for 3 min with control buffer before switching to enzyme solution (control solution containing collagenase type II (2.4 mg/mL) and 25 µmol/L CaCl₂). After perfusion, ventricles were removed, minced in control solution and incubated at 37 °C for an additional 3 min with titration. Dissociated cells were then filtered through a nylon mesh to remove big pieces of undigested tissues. Isolated cells were rinsed in control solution and allowed to settle by gravity to remove debris and non-cardiomyocytes. Calcium was added to the myocytes in step-wise fashion by settling/resuspension in 4 steps. Purified myocytes were resuspended in Medium 199 supplemented with 110 mg/L sodium pyruvate, 0.1 mmol/L β-mercaptoethanol, 100 U/mL penicillin, 100 µg/mL streptomycin, and 10% fetal calf serum and cultured on laminin-coated culture plates at a density of approximately 6000 cells/cm² at 37 °C for 2 h before washing to remove dead and non-adherent cells. Cells were maintained overnight in serum-containing medium before experimentation. Ventricular fibroblasts were isolated following the first low-speed spin to sediment myocytes. Fibroblasts were plated in Dulbecco's modified eagle medium (DMEM) plus 10% fetal calf serum and 1% penicillin/streptomycin and allowed to culture until confluence. Upon reaching confluence, the media was changed to serum-free DMEM for one hour. Cells were then washed one time with PBS and harvested for subsequent experimentation.

Western blot analysis

The LV was carefully dissected away from the right ventricle and atria, and flash-frozen in liquid nitrogen. LV were homogenized in isoelectric focusing buffer (8 mol/L urea, 2.5 mol/L thiourea, 4% Chaps, 2 mmol/L EDTA) containing 2 mmol/L tributylphosphine, 10 mmol/L DTT and protease inhibitors. The homogenate was centrifuged at 14000 g for 5 min, and the super-

natant saved for protein analyses. Protein concentration was determined using a modified protein assay (Bio-Rad) and prepared in Laemmli sample buffer (Bio-Rad). Proteins were resolved on 7.5% SDS-PAGE gels and transferred to PVDF. Following blocking in 5% bovine serum albumin for one hour at room temperature, membranes were incubated with primary antibody overnight at 4 °C. The following primary antibodies were used: Phospho-Stat3 (Tyr705) (Cell Signaling 9131; 1:1000), Stat3 (Cell Signaling 9139; 1:1000). Membranes were washed and incubated with secondary antibody for one hour at room temperature. Protein bands were visualized using a chemiluminescent substrate and autoradiography. Membranes were probed first with phospho signal transducer and activator of transcription 3 (STAT3), stripped, and then re-probed for total STAT3. Equal loading of proteins was verified by Ponceau-S staining.

Real-time RT-PCR

RNA was extracted from LV and isolated cells using standard TRIzol protocol (Thermo Fisher) and reverse transcribed using iScript cDNA synthesis kit (BioRad). For detection of murine IL-19 and IL-20R, real-time RT-PCR was performed with the iCycler My iQ using iQ SYBR Green Supermix (BioRad), normalized to the housekeeping gene 18S ribosomal RNA (18S). Primer sequences were as follows. IL-19 forward: 5'-GGCTAAAAGTATGTTTCAGTTCTCC-3', IL-19 reverse: 5'-AAATCTCTGGAGCGATGTCAG-3', IL-20R α forward: 5'-AACTGGCAGGCTGTGTATCC-3', IL-20R α reverse: 5'-TTGTCAGGTGCCTGGTTCTC-3', IL-20R β forward: 5'-CGAGGAGGGACGGAAGAATG-3', IL-20R β reverse: 5'-TACGGCCTCTCTCGATGTCA-3', 18S forward: 5'-GCCGCTAGAGGTGAAATTCTTG-3', 18S reverse: 5'-CTTTCGCTCTGGTCCGTCTT-3'. Myosin heavy chain β (MYHC β), atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), myosin heavy chain α (MYHC α), and sarcoplasmic reticulum Ca²⁺ ATPase (SERCA) oligonucleotide sequences were used as previously published^[19]. Δ Ct were calculated relative to the housekeeping gene 18S to allow comparisons across all groups (genotype and sex). As such, a lower Δ Ct indicates higher expression.

Statistical analysis

Significance was set a priori at $P < 0.05$. Data were analyzed by Students t-test using GraphPad and 2-way ANOVA (genotype by sex) using IBM SPSS Statistics Version 24. Data with unequal variance were log-transformed to meet assumptions for homoscedasticity. Data are expressed as means \pm SE of the mean. Where statistical analyses trend towards significance ($P < 0.1$), values are also noted above figures. Kaplan-Maier survival curves were generated for survival data, and differences in survival were assessed with log rank test. The statistical methods of this study were reviewed by David Kao, MD from the University of Colorado-Denver.

RESULTS

IL-19 signaling in the female dominant dnCREB model of HF

To begin to delineate the role of IL-19 in dnCREB-mediated HF, we assessed the expression of IL-19 and its receptor subunits in the LV from dnCREB mice compared to controls. Male dnCREB mice showed no change in IL-19 expression (Figure 1A); however, female dnCREB mice demonstrate significantly downregulated IL-19 expression (Figure 1A) with disease, a statistically different outcome in male and female mice (Figure 1B). Neither male nor female mice showed significant changes in expression of IL-20R α or β with disease (Figure 1C and D). However, the ratio of α/β was significantly upregulated only in female dnCREB (Figure 1E). We then assessed activation of STAT3 as a downstream mediator of IL-19 signaling. Both male and female dnCREB mice showed downregulated STAT3 activation compared to control mice (Figure 2); however female dnCREB mice STAT3 activation was suppressed to 40% of control, while male dnCREB mice were suppressed to 70% of control.

Survival of IL-19 KO and dnCREB double transgenic mice

The sexual dimorphic regulation of IL-19 and its receptor subunits in dnCREB-mediated suggests that IL-19 is cardioprotective in the setting of dnCREB, since female mice in this model suffer premature morbidity and mortality compared to males and express significantly attenuated IL-19. To test this hypothesis, we generated a novel double transgenic model (DTG) of IL-19 knockout in dnCREB-mediated HF. Survival analyses show that DTG males died from HF earlier in the development of disease than dnCREB male mice; with nearly identical survival curves to dnCREB females and female DTG (Figure 3). During this time, there was no morbidity in the Con or IL-19 KO mice (data not shown). Thus, knockout of IL-19 in this model accelerates mortality only in male mice, with no additional effect in females.

Assessment of cardiac function in DTG mice

To confirm that accelerated mortality in DTG mice is due to cardiac dysfunction, we examined contractile function in male and female DTG mice at 10 wk of age by echocardiography. Representative M-mode echocardiographs are shown in Figure 4, and quantification (no hyphen) of echocardiography is reported in Table 1. Previous reports of the dnCREB model of female-dominant HF reported diminished fractional shortening (19.4% and 8.79%) and cardiac output (17.4 and 14.6 mL/min) in male and female mice respectively, with a significant difference between sexes^[11]. Consistent with the dnCREB model, our DTG mice showed evidence of significant cardiac contractile dysfunction, with low fractional shortening (14% and 12%), stroke volume (24 and 23 μ L), and cardiac output (13.59 and 14.35 mL/

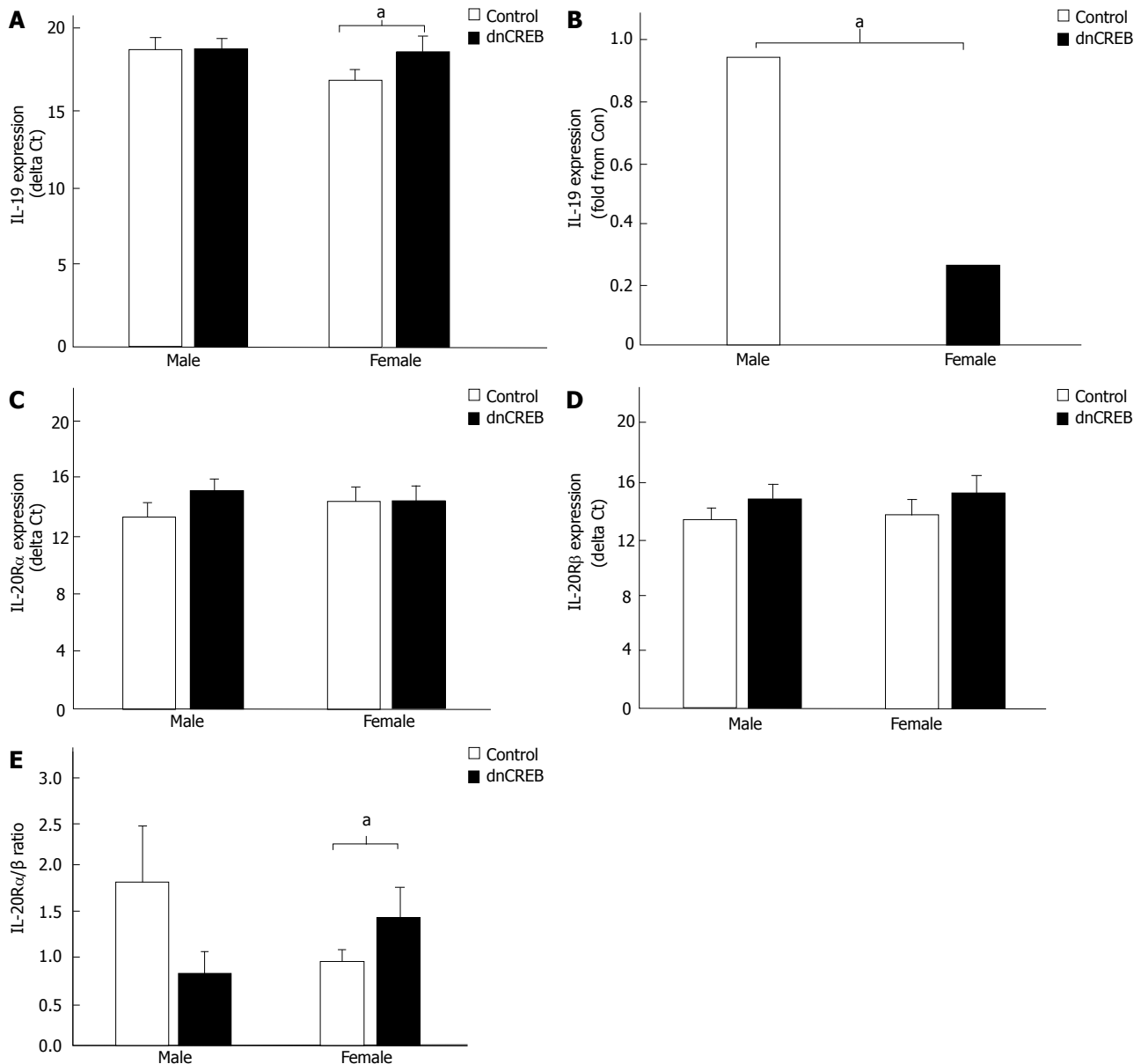


Figure 1 Expression of interleukin-19 and interleukin-20R in the dominant negative cyclic AMP response-element binding protein model of female-dominant heart failure. A: Female male significantly downregulated IL-19 expression in the setting of dnCREB-mediated heart failure compared to male mice which maintained IL-19 expression; B: A significant difference between sexes; C: IL-20Rα and IL-20Rβ (D) expression were unchanged in either sex; D: However, the ratio between IL-20Rα/β was significantly upregulated in female dnCREB mice. Expression of IL-19 and IL-20R was assessed by qRT-PCR, and ΔCt calculated relative to 18S. The ratio of IL-20Rα/β was calculated as a fold change of α-β within each sex. Data are expressed as mean ± SEM. ^a*P* < 0.05, *n* = 5-9 mice per group. dnCREB: Do-minant negative cyclic AMP response-element binding protein.

min) in male and female mice, respectively. However, genetic ablation of IL-19 completely abrogated the previously reported sex difference in the dnCREB model. That is, male DTG mice display similar levels of cardiac morbidity as female DTG, suggesting that IL-19 is cardioprotective in the dnCREB model of HF.

IL-20R expression and STAT3 activation in DTG mice

We assessed the relative expression of IL-20Rα and β subunits in DTG male and female mice. We found male and female DTG mice to express similar levels of both subunits, with no difference in the ratio of the receptor subunits (Figure 5A and B). In addition, we assessed activation of STAT3 in male and female DTG mice and

found STAT3 activation to be similar between sexes (Figure 5C and D). Expression of IL-20R and STAT3 activation in DTG male and female mice contrast with dnCREB mice, where downstream IL-19 signaling was significantly different between sexes.

Biochemical responses to dnCREB-mediated HF

We assessed the expression of five genes in the hypertrophic gene program. These genes, components of the fetal gene program, are differentially expressed in established pathologic cardiac hypertrophy. While myosin heavy chain α (MYHCα) expression was unchanged by either sex or genotype (Figure 6A), myosin heavy chain β (MYHCβ), atrial natriuretic factor (ANF) and

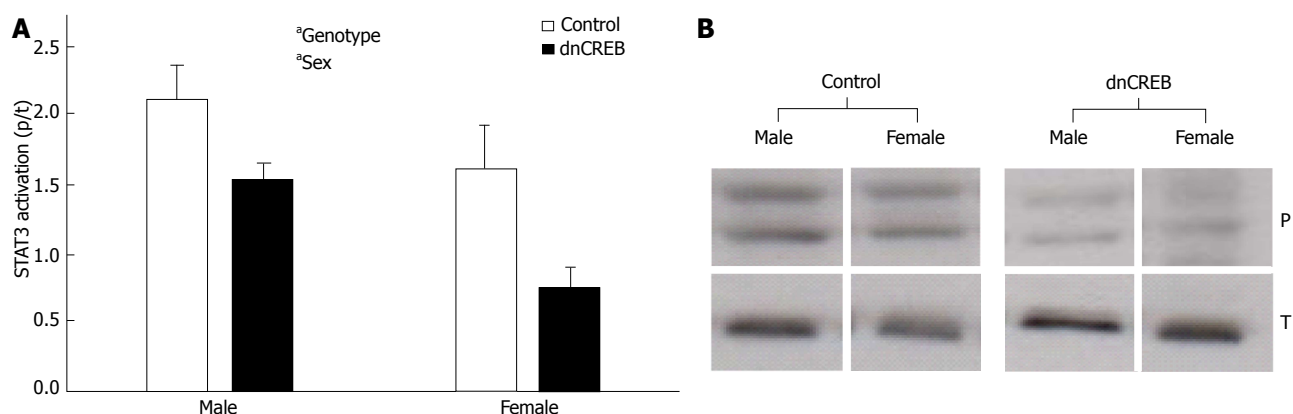


Figure 2 Activation of signal transducer and activator of transcription 3 in the dominant negative cyclic AMP response-element binding protein model of female-dominant heart failure. **A:** Male and female dnCREB mice show attenuated STAT3 activation compared to controls; **B:** Representative immunoblotting images. Activation of STAT3 was assessed by immunoblotting of phospho STAT3/total STAT3. Data are expressed as mean \pm SEM and analyzed by 2-way ANOVA. All four conditions were run on the same gel, and non-essential lanes were removed for generation of the representative images. ^a $P < 0.05$, $n = 2-6$ mice per group. ^a: Significant effect of genotype. dnCREB: Do-minant negative cyclic AMP response-element binding protein; STAT3: Signal transducer and activator of transcription 3.

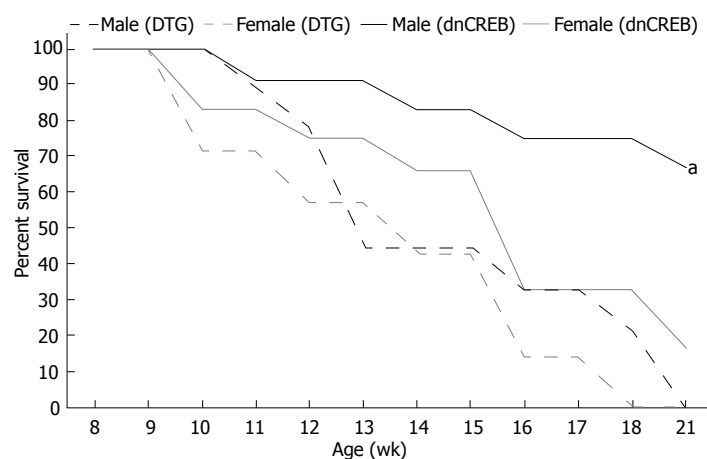


Figure 3 Kaplan-Meier survival curve of dominant negative cyclic AMP response-element binding protein and double transgenic male and female mice. IL-19 knockout in the setting of dnCREB accelerates male mouse mortality, while not affecting female dnCREB survival. No mortality was observed in Control or IL-19 KO mice during this period. Log-rank analyses were performed to compare survival between groups. ^a $P < 0.05$ vs female DTG, female dnCREB, and male DTG; $n = 7-10$ mice per group. dnCREB: Do-minant negative cyclic AMP response-element binding protein; DTG: Double transgenic.

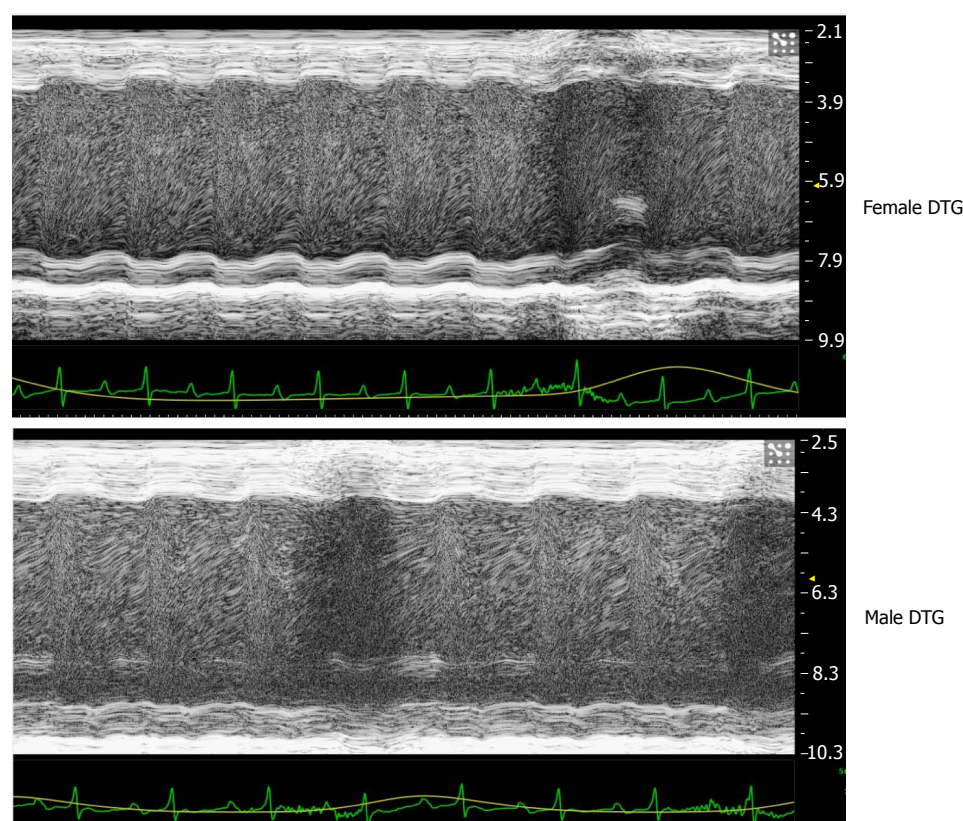


Figure 4 Representative images from M-mode echocardiographic analysis of cardiac function in male and female double transgenic mice. Quantification of echocardiographic analyses are presented in Table 1. DTG: Double transgenic.

Table 1 Cardiac function in dominant negative cyclic AMP response-element binding protein/interleukin-19 KO double transgenic male and female mice¹

		LVID; d (mm)	LVID; s (mm)	FS (%)	SV (μ L)	HR (bpm)	CO (mL/min)
DTG	Male	4.49 \pm 0.47	3.90 \pm 0.60	13.95 \pm 4.2	24.10 \pm 2.60	566 \pm 30	13.59 \pm 1.33
	Female	4.53 \pm 0.18	3.99 \pm 0.29	12.02 \pm 3.05	23.34 \pm 3.11	621 \pm 24	14.35 \pm 1.30

¹Values are presented as mean \pm SEM. Animals are 10 wk of age; $n = 3$ of each sex. All comparisons between sexes are $P > 0.05$ as assessed by Student's *t*-test. LVID; d: Left ventricular internal diameter at diastole; LVID; s: Left ventricular internal diameter at systole; FS: Fractional shortening; SV: Stroke volume; HR: Heart rate; CO: Cardiac output. DTG: Double transgenic.

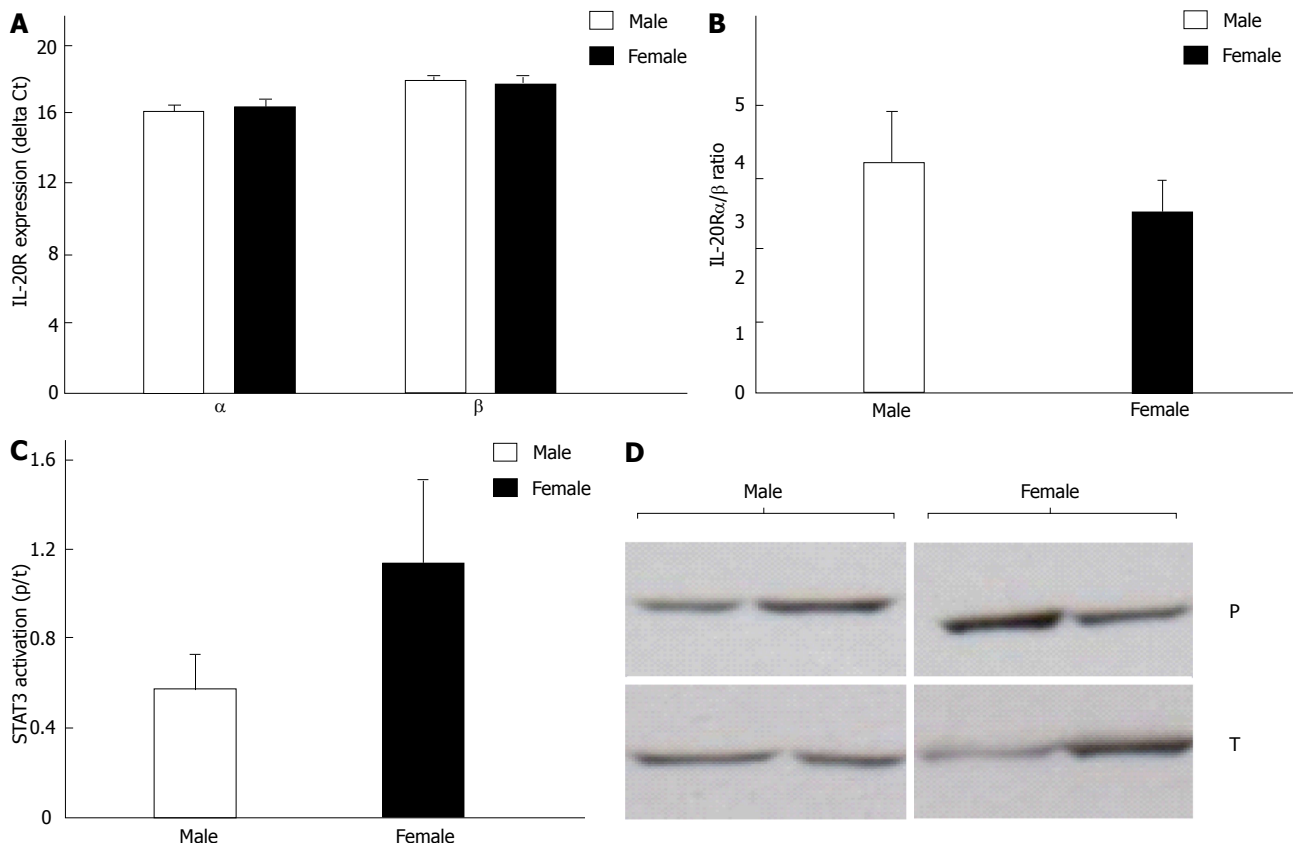


Figure 5 Expression of interleukin-20R α/β and activation of signal transducer and activator of transcription 3 in male and female double transgenic mice. A: IL-20R α and IL-20R β expression were similar in male and female DTG mice; B: Similarly, the ratio of IL-20R α/β did not differ between sexes; C: STAT3 activation did not differ between male and female DTG mice; D: Representative immunoblotting images. Expression of IL-20R was assessed by qRT-PCR and expressed as Δ Ct calculated relative to 18S. The ratio of IL-20R α/β was calculated as a fold change of α/β within each sex. Activation of STAT3 was assessed by immunoblotting of phospho STAT3/total STAT3. Both male and female mice were run on the same gel, and non-essential lanes were cropped for generation of the representative image. Data are expressed as mean \pm SEM; $n = 4-7$ mice per group. STAT3: Signal transducer and activator of transcription 3; DTG: Double transgenic.

brain natriuretic peptide (BNP) were all significantly upregulated in dnCREB and DTG mice (Figure 6B-D), while sarcoplasmic reticulum Ca²⁺ ATPase (SERCA) expression was significantly downregulated (Figure 6E). Surprisingly, we observed no overall effect of sex on fetal gene program expression; however, BNP expression was more robustly induced in female dnCREB mice compared to male dnCREB (4.8 fold vs 2.6 fold, $P < 0.05$, data not shown).

Expression of IL-19 and IL-20R in isolated cardiac myocytes and fibroblasts

IL-19 signaling is uncharacterized in the heart. It is

imperative we understand IL-19 signaling in the male and female heart to understand the dysregulation that occurs with disease. Therefore, we isolated primary cardiac myocytes and fibroblasts from male and female mice to assess IL-19 signaling in these two cell types. Both fibroblasts (Cfib) and myocytes (CM) expressed IL-19, with no differences between sexes in either cell type (Figure 7A). Both cell types also express IL-20R α , with higher expression in CM than Cfib, and a trend towards lower expression in female myocytes than males (Figure 7B). Fibroblasts and myocytes similarly express IL-20R β , with no difference between sexes (Figure 7C), however the ratio of IL-20R α/β

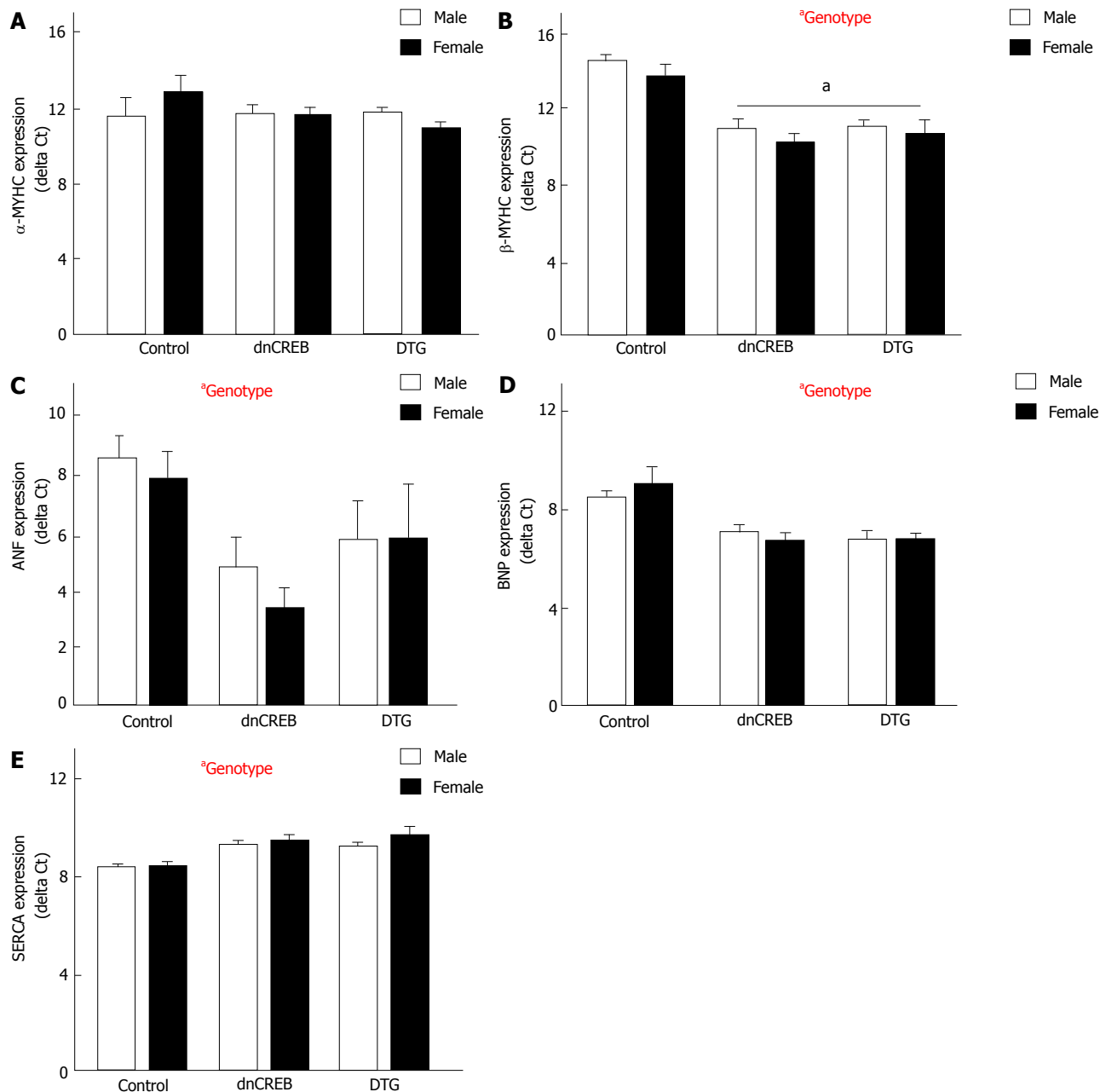


Figure 6 Activation of the fetal hypertrophic gene program in dominant negative cyclic AMP response-element binding protein and double transgenic mice. A: Myosin heavy chain α (MYHC α) expression was unchanged by either sex or genotype; B: Myosin heavy chain β (MYHC β); C: Atrial natriuretic factor (ANF); D: Brain natriuretic peptide (BNP) were all significantly upregulated in both male and female dnCREB and DTG mice; E: Sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) expression was significantly downregulated in both sexes with disease. Expression of fetal hypertrophic genes was assessed by qRT-PCR, relative to the housekeeping gene 18S. Data are expressed as mean \pm SEM and assessed by 2-way ANOVA. $^aP < 0.05$ vs Control; $n = 4-7$ mice per group. a: Significant effect of genotype. dnCREB: Do-minant negative cyclic AMP response-element binding protein; DTG: Double transgenic.

was significantly higher in CM than Cfib (Figure 7D), suggesting the potential for cell-type specific responses to IL-19 signaling in the heart.

DISCUSSION

HF is a sexually dimorphic disease, adversely affecting female patients regarding morbidity and mortality. The maladaptive role of cytokines in HF is well documented; however, only a few studies have considered sex differences in cytokine expression or signaling. We show for the first time that IL-19, a previously

undescribed cytokine in the heart, is expressed in rodent cardiac tissue and two previously unexamined cardiac cell types: Cardiac myocytes and fibroblasts. Further, we report dysregulation of IL-19 signaling in a female-dominant model of HF, suggesting a cardioprotective role of IL-19 in the heart. We propose the following model, as summarized in Figure 8, where IL-19 signaling through IL-20R α/β activates STAT3 and canonical downstream cardioprotective mechanisms. This pathway is significantly downregulated in female dnCREB mice, resulting in attenuated STAT3 activation, LV remodeling, cardiac dysfunction, and premature

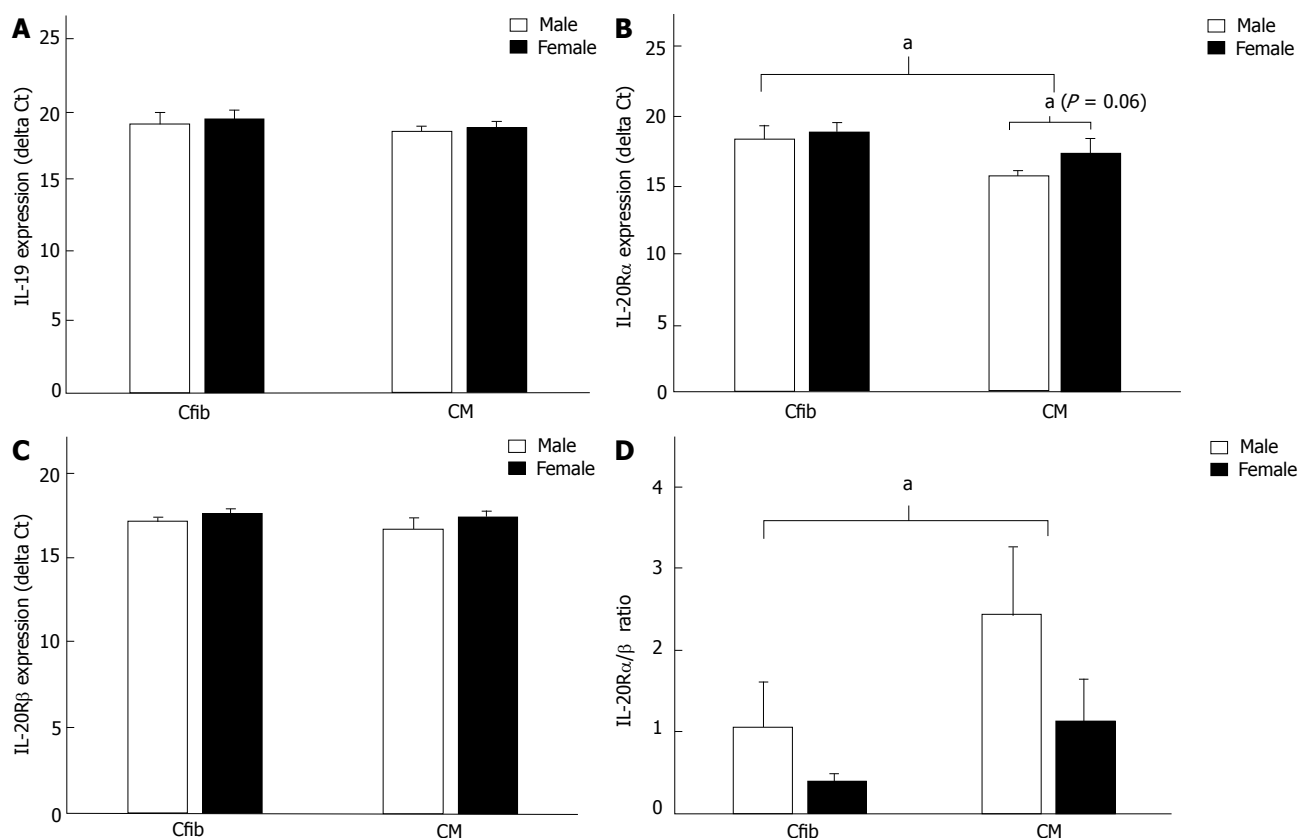


Figure 7 Interleukin-19 and interleukin-20R expression in male and female cardiac fibroblasts and myocytes. A: Both male and female Cfib and CM express IL-19, with no differences between sexes or cell types; B: Both Cfib and CM express IL-20R α , with higher expression in CM than Cfib, as evident by the lower delta Ct. Male CM tended to express higher IL-20R α than female CM ($P = 0.06$); C: Both Cfib and CM express IL-20R β , with no differences between cell types or sex; D: The ratio of IL-20R α / β was significantly higher in CM than Cfib. IL-19 and IL-20R expression were assessed by qRT-PCR and normalized to the housekeeping gene 18S. Data are expressed as mean \pm SEM and assessed by 2-way ANOVA; $n = 7-8$ mice per group. Cfib: Cardiac fibroblasts; CM: Cardiac myocytes.

mortality. However, male dnCREB mice maintain IL-19 expression with disease, resulting in heightened cardioprotection and significantly less morbidity and mortality compared to female mice. Ongoing investigations will elucidate further mechanistic insight into sexually divergent downstream IL-19 mediated cardiac signaling and whether this novel cytokine represents a new therapeutic target for the treatment of women's heart disease.

IL-19 was first discovered over a decade ago and classified as a member of the IL-10 family based on structure and location of the IL-19 gene and the use of similar receptor complexes^[20]. Since its discovery, however, the function of IL-19 has remained unclear. In a number of disease states including asthma^[21], sepsis^[22], and acute kidney injury^[23] IL-19 acts as a pro-inflammatory factor. Conversely, in inflammatory bowel disease^[17] and vascular disease^[24], IL-19 appears to be anti-inflammatory and protect against disease progression. These data imply that IL-19 may function as either pro- or anti-inflammatory depending on the tissue and disease context. Further, it suggests that downstream IL-19 signaling including receptor subunit expression may be implicated in the disparate biological outcomes. A study examining IL-20R expression in 24 different human tissues reports significant differential α /

β subunit expression between tissue types^[9] suggesting differential relative expression of these two subunits may be implicated in the varying biological outcomes of IL-19 signaling. Various groups have attempted to define the binding kinetics and receptor requirements for IL-19 signaling. While most report a requirement for the IL-20R heterodimer and the rapid formation of a stable 1:1:1 complex in the presence of a ligand, other evidence also supports less stable homodimer formation^[25]. In support of homodimer IL-20R signaling, IL-19 has clear effects on lymphocytes derived from IL-20R β knockout mice^[26]. Thus the specific requirement for receptor dimerization remains controversial, as does the effect of subunit expression on IL-19 downstream function. We assessed IL-20R subunit expression in isolated primary cardiac myocytes and fibroblasts and found differential expression of the receptor subunits, suggesting that IL-19 may modulate IL-20R in a cell-type specific manner. These data are consistent with previous reports of IL-19 signaling in the vasculature which demonstrate that IL-19 stimulation of vascular smooth muscle cells induces expression of IL-20R β with no effect on endothelial cells^[27]. Further, receptor subunit expression may be regulated in a sex-specific manner during disease progression as evidenced by differential IL-20R α / β ratios in male and female dnCREB

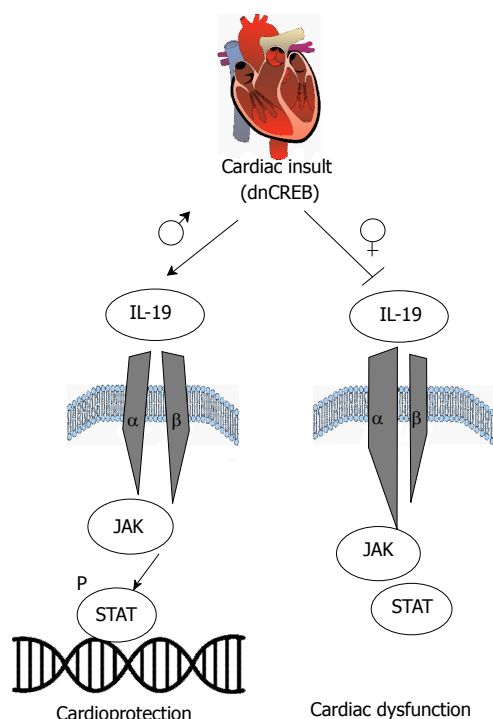


Figure 8 Working model of interleukin-19 in sex-specific heart failure. Cardiac insult (inactivation of cyclic AMP response-element binding protein) results in maintained interleukin-19 (IL-19) expression in male mice, with maintained expression of IL-20 receptor subunits. Activation of downstream JAK-STAT signaling in male hearts is cardioprotective. However, cardiac insult in female mice results in attenuated IL-19 signaling, dysregulated expression of IL-20R subunits, and cardiac dysfunction. Ongoing investigations will delineate the downstream mediators implicated in IL-19 cardioprotection in a sex-specific manner.

mice. Together, these data suggest that cell and context-specific regulation of IL-20 receptor isoforms may be important in disease, and may do so in a sexually dimorphic manner. Elucidation of the effects of IL-19 on specific cardiac cell populations (including inflammatory cells, endothelial, and vascular smooth muscle unexamined here) from male and female models warrants future investigation.

IL-19 treatment of IL-20R α/β expressing cells leads to tyrosine phosphorylation of STAT3^[28]. STAT3 is universally cardioprotective in response to a number of cardiac insults including ischemia-reperfusion injury^[29] and hypertrophy^[30]. Myocyte-specific STAT3 knockout mice develop cardiac fibrosis and myocardial dysfunction even in the absence of stress^[31]. These mice are also more susceptible to inflammation-induced cardiac damage and greater contractile dysfunction^[32], and ultimately lack of myocyte STAT3 leads to age-related HF^[31,32]. Furthermore, human failing hearts exhibit reduced STAT3 levels and activity compared to healthy controls^[33]. Thus, STAT3 is crucial for cardiac resistance to inflammation and other acute injuries. We show attenuated STAT3 activation in the LV from dnCREB male and female mice. Further, this effect is more robust in female dnCREB mice, correlating with the female-dominance of the dnCREB model and the early mortality of female mice. The mechanisms

of STAT3-mediated cardiac protection in our model are not yet characterized; though canonical (Tyr705) STAT3 activation has proposed anti-oxidant, anti-apoptotic, and pro-angiogenic target genes (Reviewed in^[34]). In addition, STAT3 also enhances mitochondrial respiration and acts on complex I to inhibit reactive oxygen species formation; mechanisms which are augmented by non-canonical phosphorylation of STAT3 at Ser727^[35]. The action of STAT3 on mitochondrial function is particularly interesting and warrants future investigation, as dnCREB female mice have increased oxidant production, attenuated antioxidant defenses, and disrupted mitochondrial structure and function compared to male dnCREB^[11].

In summary, we show for the first time that IL-19 demonstrates clear sexually dimorphic expression in the female-dominant dnCREB model of HF. Ablation of IL-19 in this model accelerates male mortality and causes severe cardiac morbidity, suggesting a cardioprotective role for IL-19 in the heart. Elucidation of IL-19 signaling in this model and in other models of female-dominant HF will facilitate the identification of novel therapeutics for women's heart disease.

ACKNOWLEDGMENTS

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COMMENTS

Background

Heart failure (HF) is a sexually dimorphic disease, with worse morbidity and mortality in female patients compared to males. Inflammation is hypothesized to play a detrimental role in HF development, though whether it is regulated in a sexually dimorphic manner remains unknown. Interleukin-19 (IL-19) is an inflammatory cytokine with an unknown function in the healthy heart or in HF. Therefore, the authors set out to assess the role of IL-19 in female dominant HF.

Research frontiers

HF is characterized by inflammatory signaling, though how this may be regulated in a sex-specific manner is unknown. Since HF is a sexually dimorphic disease, it is imperative that understand molecular mechanisms which contribute to disease in a sex-specific approach.

Innovations and breakthroughs

Although IL-19 has been studied in the vasculature, few reports exist regarding cardiac signaling. The authors show for the first time that IL-19 demonstrates clear sexually dimorphic expression in a model of female-dominant HF. Genetic ablation of IL-19 in this model accelerates male mortality, suggesting IL-19 is cardioprotective.

Applications

Development of sex-specific therapies will improve HF outcomes, and is a primary goal of personalized medicine. To develop sex-specific therapies, the authors must understand mechanisms which underlie HF in both males and females. Although the impact of IL-19 in the human heart remains unknown, the data identify sex-specific mediators of cardiac function, and suggest that therapies for the failing human heart be explored in both sexes.

Peer-review

This is a very interesting topic. The paper is well written, clear and interesting. The results provide adequate grounds for the conclusion.

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Case Control Study

Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure

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Abstract**AIM**

To test the safety and effectiveness of hypertonic saline solution (HSS + F) as a strategy for weight loss and

prevention of further deterioration of renal function.

METHODS

Patients admitted with acute decompensated heart failure (ADHF) who received HSS + F were included in the study. After a period of a standard ADHF treatment, our patients received an intravenous infusion of furosemide (250 mg) combined with HSS (150 mL of 3% NaCl) twice a day for a mean duration of 2.3 d. Our primary outcomes were weight loss and a change in serum creatinine per day of treatment. The parameters of the period prior to treatment with HSS + F were compared with those of the period with HSS + F.

RESULTS

A total of 47 patients were included. The mean creatinine on admission was $155 \mu\text{mol/L} \pm 65 \mu\text{mol/L}$, the ejection fraction was $40\% \pm 17\%$. The experimental treatment (HSS + F) resulted in greater weight loss per day of treatment than the standard treatment ($-1.4 \text{ kg/d} \pm 1.4 \text{ kg/d}$ vs $-0.4 \text{ kg/d} \pm 1.0 \text{ kg/d}$, $P = 0.0168$). Importantly, the change in creatinine was not significantly different.

CONCLUSION

This study supports the effectiveness of HSS + F on weight loss in patients with ADHF. The safety profile, particularly with regard to renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

Key words: Heart failure; Decompensated; Hypertonic saline; Renal failure; Fluid overload

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Core tip: Hypertonic saline solution (HSS) has been proposed in recent years as a potential therapy to facilitate diuresis in patients with decompensated heart failure and to overcome diuretic resistance. This study supports the effectiveness of HSS + F on weight loss in patients with acute decompensated heart failure and a high burden of comorbidities, despite a proportion of patients having preserved ejection fraction, right heart failure and advanced renal failure. The administration of small intravenous boluses of HSS in conjunction with intravenous furosemide can be a feasible and inexpensive therapeutic option which can prevent the use of costlier and more invasive treatments such as ultrafiltration, hemodialysis and inotropic infusion.

Lafrenière G, Béliveau P, Bégin JY, Simonyan D, Côté S, Gaudreault V, Israeli Z, Lavi S, Bagur R. Effects of hypertonic saline solution on body weight and serum creatinine in patients with acute decompensated heart failure. *World J Cardiol* 2017; 9(8): 685-692 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/685.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.685>

INTRODUCTION

Heart failure (HF) is a well-recognized major public health problem affecting about 26 million people worldwide^[1]. Its impact in terms of mortality, morbidity, quality of life and cost is considerable. Acute decompensated heart failure (ADHF) is a leading cause of hospitalization and a common issue in emergency departments. Loop diuretics have long been recognized as the key for the treatment of ADHF^[2], however, high doses can cause adverse effects, including electrolyte abnormalities and deterioration of renal function. In addition, patients can develop resistance to diuretics and congestive symptoms can persist despite treatment with high doses^[3]. Currently available treatment options include higher doses or a continuous infusion of intravenous diuretics^[4,5], a combination of different classes of diuretics for their synergistic effects^[6,7], and in severe/advanced cases, parenteral inotropes^[8-10] and ultrafiltration^[11,12]. The last two options are not associated with a better prognosis, and in fact, can cause deleterious effects and their use is limited by the cost and availability^[11-14].

The hypertonic saline solution (HSS) has been proposed in recent years as an adjunctive therapy for intravenous loop diuretics to improve or restore their initial pharmacological efficacy^[3]. Among the proposed mechanisms to explain the benefits of HSS, it has been reported that it would prevent intravascular depletion due to diuretics^[15,16] and thus would maintain renal flow and the glomerular filtration rate (GFR) during intensive treatment of intravenous furosemide^[17].

Compared to the administration of high doses of intravenous furosemide alone, concomitant use of HSS (HSS + F) has shown, in patients with ADHF, a more rapid and complete resolution of the signs and symptoms of congestion by increasing urine volume and by potentiating weight loss^[16,18,19], the potential to protect against deterioration of renal function during intensive diuretic therapy^[15,20], an improvement of cardiac biomarkers and echocardiographic parameters^[19,21,22], a reduced length of hospital stay and frequency of re-hospitalizations^[23] and a good safety profile^[24].

Therefore, the aim of the present report was to test the safety and effectiveness of HSS + F as a strategy for weight loss and prevention of further deterioration of renal function compared to the usual intensive treatment with intravenous furosemide alone.

MATERIALS AND METHODS

Patients admitted with ADHF and who received HSS + F between January 2012 and December 2013 at the Quebec University Hospital Centre were included for the analysis. The decision to prescribe HSS + F following the standard treatment for a given patient was left to the discretion of the treating cardiologist,

Eligible patients
Men or women older than 18 years
ADHF with congestive symptoms and signs
Refractory to standard treatment of ADHF
Worsening renal function due to increased diuretics doses
Poor responsiveness to treatment with furosemide
Constant increase of body weight
Persistence of peripheral or pulmonary edema
Reduction of urine volume
Orthostatic hypotension with increased diuretic doses
Patients who should not receive protocol
Hypertensive crisis
Baseline hyponatremia
No congestive symptoms and signs
Prescription protocol
Infusion of HSS + F: 150 mL of 3% NaCl + 250 mg of furosemide
Administered over one hour
Twice a day for a suggested period of 48 h
Other prescriptions
Fluid restriction of 1.5 L/d
Vital signs and weight must be recorded daily
Serum Na, serum K and creatinine must be recorded daily

Figure 1 Study protocol. ADHF: Acute decompensated heart failure; HSS: Hypertonic saline solution.

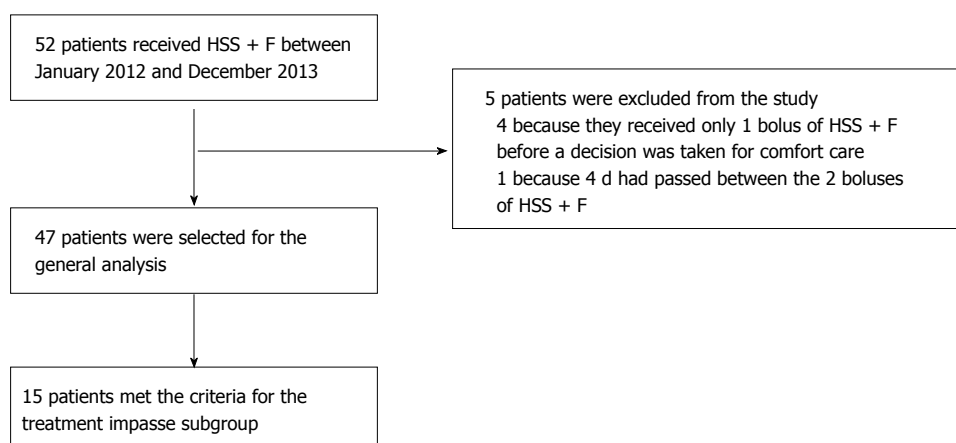


Figure 2 Data collection protocol and observation periods.

who had received at the beginning of the study a list of the suggested inclusion and exclusion criteria (Figure 1). All clinical, echocardiographic and laboratory data were prospectively collected in a dedicated database. Institutional review board approval and patient consent were not required because of the nature of this study.

Intervention

On admission for ADHF, most patients were on fluid restriction of 1.5 L/d, received an intravenous furosemide dose that was adjusted according to the clinical response and the conventional HF treatment that was considered appropriate by the treating physician based on current recommendations^[25,26]. When patients were considered to be refractory to this treatment, based on a poor response to standard therapy (weight, creatinine, clinical judgment), intravenous furosemide was replaced by an intravenous infusion of HSS + F (150 mL of 3% NaCl + 250 mg of furosemide) administered

over one hour twice a day for a suggested period of 48 h that could be extended or shortened depending on the clinical response. Patients underwent the usual daily medical examination for the evaluation of the signs and symptoms of HF. Vital signs and weight were recorded daily; serum creatinine, sodium (Na) and potassium (K) levels were closely monitored during treatment. Moreover, the clinician's impression concerning the treatment effectiveness was recorded in the medical notes. Patients were all compared to themselves with a before and after study design. The effects of treatment with intravenous furosemide alone (standard treatment) were compared to the treatment with intravenous furosemide plus HSS (HSS + F) (experimental treatment) administered following the standard treatment. The results available from days one to four prior to the initiation of saline treatment were analyzed and compared to the experimental treatment d (Figure 2).

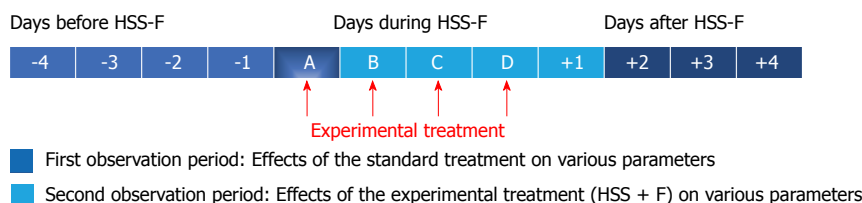


Figure 3 Flow diagram of participants in the study. HSS: Hypertonic saline solution.

Outcomes

Our primary outcomes were the decrease in weight and the change of creatinine per day of treatment. Secondary outcomes were the effect of the experimental treatment on the serum Na and K levels and its safety profile regarding neurological events.

Subgroup analysis

The effects of HSS + F on weight and creatinine were studied in the “treatment impasse” subgroup defined as all patients with increased weight and creatinine per day of treatment despite standard therapy.

Statistical analysis

Continuous data are presented as mean \pm SD or median [interquartile range (IQR)] depending on variable distribution, and categorical data are presented as frequencies (percentage). Differences between the weight reduction in the experimental treatment and the standard treatment periods were assessed by Wilcoxon Signed Rank test for paired samples. The same approach was used for all other analyses as the change of creatinine per day of treatment between these two periods and analyses in the “treatment impasse” subgroup. The level of statistical significance was set as $P < 0.05$. Data were analyzed using the SAS statistical software, version 9.3.

RESULTS

A total of 52 patients received HSS + F for ADHF. Five patients were excluded from the study; four because they received one bolus of HSS + F before the decision of giving end-of-life comfort care only, and one patient was not selected because four d had elapsed between the two boluses of HSS + F, making interpretation difficult.

Hence, a total of 47 patients (32 men, 68%), mean age of 77.6 ± 9.5 years, were included in the study (Figure 3). Thirty-two (68%) patients had chronic kidney disease based on an estimated GFR (eGFR) ≤ 60 mL/min per 1.73 m^2 . Moreover, the mean creatinine was $155 \pm 65 \text{ } \mu\text{mol/L}$, leading to an eGFR of 42 ± 22 mL/min per 1.73 m^2 on admission. Of note, 12 (25.5%) presented with a serum Na $< 135 \text{ mmol/L}$. The left ventricle ejection fraction (LVEF) was $40\% \pm 17\%$ and half of the patients had $\leq 40\%$ (Table 1). In addition, 31 patients had pleural effusion, 11 had ascites, 11 presented with arterial hypotension and/or orthostatic

hypotension and 13 had acute kidney injury defined as a 1.5-fold increase in serum creatinine or absolute increase in serum creatinine of $\geq 26.4 \text{ } \mu\text{mol/L}$ from their baseline value^[27,28].

Before receiving HSS + F, six (12.8%) patients required non-invasive ventilation and three (6.4%) patients were intubated for respiratory failure, but no form of mechanical ventilation was initiated during treatment with HSS + F. In addition, eight (17%) patients had a thoracentesis during hospitalization (two during the HSS + F treatment period and six outside of the observation period) and four (8.5%) patients had a paracentesis (two during the standard treatment and none during the HSS + F treatment). Moreover, eight (17%) patients received an infusion of inotropes, but only three during the observation period (one during the experimental treatment, one throughout the two treatments studied and the remaining during the standard treatment only). Six (12.8%) patients underwent coronary angiography during hospitalization, but only two patients had it during the observation period (one during the standard treatment and the other had two coronary angiograms: One before and another during treatment with HSS + F).

Intervention

Patients received a mean of 5.1 ± 2.0 doses of HSS + F for a mean duration of 2.3 ± 1.0 d. During the treatment period with HSS + F, patients lost 3.9 ± 3.8 kg. Interestingly, the treating physician reported a significant improvement in signs and symptoms of congestion with this experimental treatment on 38 (81%) patients. In addition, weight loss per day of treatment was significantly greater with HSS + F treatment than with the standard treatment ($-1.4 \pm 1.4 \text{ kg/d}$ vs $-0.4 \pm 1.0 \text{ kg/d}$, mean difference of $0.8 \pm 1.8 \text{ kg/d}$, $P = 0.0168$) (Table 2). The change in creatinine per day of treatment was not statistically different between treatments (Table 2). The mean serum Na increased by 2.4 mmol/L (95%CI: $1.6\text{--}3.1$, $P < 0.0001$) and the mean serum K decreased by 0.2 mmol/L (95%CI: -0.4 to -0.1 , $P = 0.0001$) with the experimental treatment compared to the standard treatment. The mean daily dose of intravenous furosemide given during the standard treatment period was 106 ± 67 mg. Four patients received an additional continuous infusion of furosemide for a mean duration of 2.3 d. Nine patients received mainly oral furosemide, with a correspondingly larger mean daily

Table 1 Baseline characteristics of the study population *n* (%)

Variables	<i>n</i> = 47
Age (yr)	77.6 ± 9.5
Males	32 (68.1)
Body mass index (kg/m ²)	28.2 ± 7.2
Hypertension	46 (97.9)
Diabetes	28 (59.6)
NYHA functional class (admission)	
III	16 (38.1)
IV	23 (54.8)
Coronary artery disease	33 (70.2)
Ischemic heart failure	29 (61.7)
Stroke or transient ischemic attack	11 (23.4)
Vascular disease	22 (46.8)
Atrial fibrillation	27 (57.4)
Oxygen-dependent COPD	4 (8.5)
Active cancer	11 (23.4)
Baseline creatinine (μmol/L) ¹	140.1 ± 65.5
Chronic kidney disease (eGFR ≤ 60 mL/min per 1.73 m ²) ¹	32 (68.1)
Admission creatinine (μmol/L)	154.8 ± 65.4
Admission eGFR using MDRD (mL/min per 1.73 m ²)	42.2 ± 22.3
Admission serum Na concentration < 135 mmol/L	12 (25.5)
Echocardiographic data	
Left ventricle ejection fraction	39.9 ± 17.4
LVEF > 40%	23 (48.9)
LVEF ≤ 40%	24 (51.0)
Severe aortic stenosis	1 (2.2)
Moderate and/or severe mitral regurgitation	16 (34.8)
Severe tricuspid regurgitation	6 (13.0)
Pulmonary hypertension ≥ 50 mmHg	19 (41.3)
Severe diastolic dysfunction	11 (23.9)
Right ventricular dysfunction/dilatation	28 (60.9)
Medications	
ACEI/ARBs	28 (59.6)
Hydralazine	3 (6.4)
Beta-blocker	39 (83.0)
Diuretics	
Oral furosemide	39 (83.0)
Thiazide	9 (19.1)
Spironolactone	8 (17.0)
Zaroxolyn	1 (2.1)
Furosemide dose per day (mg)	128.2 ± 106.7

¹Average of the five most recent creatinine values before hospitalization. Values are expressed as mean ± SD or *n* (%). NYHA: New York Heart Association; COPD: Chronic obstructive pulmonary disease; eGFR: Estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease equation; LVEF: Left ventricle ejection fraction; ACEI: Angiotensin-converting-enzyme inhibitor; ARBs: Angiotensin II receptor blockers.

dose of 196 ± 165 mg. Seven doses of metolazone were given during the standard treatment and 7 doses during the experimental treatment.

The administration of HSS + F was well tolerated by all patients and no major adverse events were observed. It is noteworthy to be highlighted that there was no pulmonary congestion or neurological consequences due to HSS + F strategy. However, the HSS + F treatment was discontinued in 2 (4.3%) patients due to an excessive increase in serum Na (*i.e.*, from 120 mmol/L to 128 mmol/L) in 1 patient and a significant decrease in blood pressure for the other.

A total of 7 (15%) patients died during the hospital stay. The median time between death and the end

Table 2 Weight loss and creatinine change per day of treatment (*n* = 47)

Variable	mean ± SD	95%CI	<i>P</i> value
Weight loss (kg/d)			
Standard treatment	-0.39 ± 1.02	(-0.77, -0.03)	
Experimental treatment	-1.43 ± 1.43	(-1.86, -1.02)	
Standard-experimental difference	0.80 ± 1.77	(0.15, 1.44)	0.0168
Change in creatinine (μmol/L per day)			
Standard treatment	3.48 ± 9.89	(0.51, 6.68)	
Experimental treatment	-0.69 ± 9.62	(-3.51, 2.00)	
Standard-experimental difference	4.20 ± 14.25	(-0.49, 8.88)	0.331

of treatment with HSS + F was 3 (IQR: 1-33) d. However, two of these deaths were attributed to a shift to end-of-life palliative care requested by the family (treatment with HSS + F originally scheduled for 48 h was discontinued). The average hospital stay was 20 ± 12 d with a median of 16 (IQR: 11-24) d.

Notably, in the impasse treatment subgroup (*n* = 15), consisting of patients selected because of their negative response to the standard treatment, in addition to a significant weight loss achieved with the experimental treatment (-1.2 kg/d ± 1.3 kg/d vs -0.3 kg/d ± 0.6 kg/d with the standard treatment, mean difference of 1.5 kg/d ± 1.7 kg/d, *P* = 0.0026), there was an increase in creatinine level with the standard therapy that was not seen with the experimental therapy; indeed, the mean creatinine difference was also statistically significant (11 ± 13 μmol/L per day, *P* = 0.008) (Table 3).

DISCUSSION

In a population of patients admitted with ADHF, the administration of HSS + F led to a greater weight loss per day of treatment compared to the standard intravenous furosemide strategy; even if a considerable proportion of them presented HF with preserved LVEF and/or advanced renal failure.

The difference in weight loss achieved through treatment with HSS + F is comparable to that demonstrated in previous studies^[16,18,19,21-23,29,30]. Among these studies, the difference between the average in weight loss in the group treated with HSS + F compared to the group treated with intravenous furosemide alone ranged from 0.3-5.6 kg^[21,30]. Because patients generally had some weight loss with the treatment with intravenous furosemide alone before starting treatment with HSS + F, it is possible that we have underestimated the weight loss due to HSS + F that could have been achieved without the prior use of intravenous furosemide alone.

We were unable to demonstrate a statistically significant difference in terms of creatinine, although it tended to decrease with the experimental treatment while the trend was reversed with the standard treatment. It has been previously shown an increase in

Table 3 Weight loss and creatinine change per day of treatment in the impasse subgroup (*n* = 15)

Variable	mean ± SD	95%CI	P value
Weight loss (kg/d)			
Standard treatment	0.25 ± 0.64	(-0.04, 0.58)	
Experimental treatment	-1.20 ± 1.30	(-1.89, -0.57)	
Standard-experimental difference	1.45 ± 1.65	(0.54, 2.36)	0.0026
Change in creatinine (μmol/L per day)			
Standard treatment	7.33 ± 8.65	(3.01, 11.70)	
Experimental treatment	-3.79 ± 11.34	(-10.41, 1.63)	
Standard-experimental difference	11.13 ± 13.29	(3.77, 18.49)	0.008

creatinine among those treated with intravenous furosemide alone, while there is either a decrease in creatinine in patients treated with HSS + F^[16,18,22,23] or a mild increase that is less than furosemide alone^[19,21,30]. It is noteworthy to be outlined that the lack of statistical significant in creatinine levels may be explained in part by the inclusion of patients with advanced renal failure. Indeed, Engelmeier *et al.*^[29] recruited patients with advanced renal failure (eGFR < 40 mL/min) and did not demonstrate a significant advantage of using HSS for the prevention of worsening renal function. Moreover, another study showed that HSS affords a protective role in the deterioration of renal function induced by loop diuretics, but does not exert a substantial protective effect in patients with ADHF who have pre-existing advanced renal failure and exhibiting a mean creatinine ≥ 194 μmol/L^[15]. However, in our study, the renal function of many patients worsened during treatment with intravenous furosemide alone, so the change in creatinine during treatment with HSS + F could be a reflection of the previous treatment.

Treatment with HSS + F was well tolerated and its safety profile was reassuring as demonstrated in previous studies^[18,24]. Of note, although we did not adjust the Na concentration in the HSS depending on the patient's serum Na as done in most studies, there were no severe electrolyte disturbances, except in one patient who had an increase in serum Na of 8 mmol/L within 24 h, but without any neurological symptoms or further consequences. Our results indicate that serum Na levels should be monitored, but adjusting the tonicity of the HSS based on the serum Na level may not be necessary. This facilitates the administration of HSS and reduces the risk of errors.

The result for the impasse subgroup, with few available treatment options, is of particular interest. Those patients, who increased their weight and creatinine while treated with intravenous furosemide alone, had benefited from the therapy in terms of weight loss and renal function.

The use of parenteral inotropes in a number of patients hospitalized for HF is potentially deleterious and requires tighter monitoring^[31]. Moreover, the treatment of advanced ADHF by ultrafiltration or intravenous inotropes is not associated with a better prognosis and is limited

by the cost and availability^[11-14]. Therefore, according to some studies^[19,30], simultaneous administration of appropriate doses of HSS during treatment with intravenous diuretics reduce diuretic resistance, which in fact, is the phenomenon of a decrease in the natriuretic response and thus, requires the use of further increasing doses of diuretics that often results in the deterioration of renal function^[3]. Hence, the administration of small intravenous boluses of HSS associated with intravenous furosemide is a valid and inexpensive therapeutic option.

Limitations

The main limitation of this study lies with the fact of a small sample size and even prospective, the non-randomized nature of the study. Therefore, the fact that certain clinical variables that appeared to account more frequently in some group but finally did not reach statistical significance were related to the small sample size. Patients were compared to themselves under the standard and experimental treatments, and the latter being influenced by the previous one. In addition, since the standard treatment was at the discretion of the clinician, the doses of furosemide, the doses of other drugs and the use of thoracentesis or paracentesis were not the same for both treatments. Thus, confirming these results in a larger series of randomized patients might have a high impact on patient selection and clinical decision-making in this high-risk group of patients.

In conclusion, the results of this study support the effectiveness of HSS + F on weight loss. The safety profile, particularly with regard to renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

COMMENTS

Background

Compared to the administration of high doses of furosemide monotherapy, the concomitant use of hypertonic saline solution (HSS + F) has shown, in some single-centre studies, clinical benefits and a good safety profile in patients with acute decompensated heart failure (ADHF).

Research frontiers

Patients can develop resistance to diuretics and congestive symptoms may persist despite treatment with high doses of furosemide.

Innovations and breakthroughs

This study supports the effectiveness of HSS + F on weight loss in patients with ADHF.

Applications

The safety profile, particularly regarding renal function, leads us to believe that HSS + F may be a valuable option for those patients presenting with ADHF who do not respond to conventional treatment with intravenous furosemide alone.

Terminology

This study aims to test the safety and effectiveness of HSS + F as a strategy for

weight loss and prevention of further deterioration of renal function.

Peer-review

This is a well-written manuscript about the treatment of severe acute heart failure.

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Observational Study

Estimating pressure gradients by auscultation: How technology (echocardiography) can help improve clinical skills

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Abstract

AIM

To extend our previously-published experience in estimating pressure gradients (PG) *via* physical examination in a large patient cohort.

METHODS

From January 1, 1997 through December 31, 2009, an attending pediatric cardiologist compared clinical examination (EXAM) with Doppler-echo (ECHO), in 1193 patients with pulmonic stenosis (PS, including tetralogy of Fallot), aortic stenosis (AS), and ventricular septal defect (VSD). EXAM PG estimates were based primarily on a murmur's pitch, grade, and length. ECHO peak instantaneous PG was derived from the modified Bernoulli equation. Patients were 0-38.4 years old (median 4.8).

RESULTS

For all patients, EXAM correlated highly with ECHO: ECHO = 0.99 (EXAM) + 3.2 mmHg; $r = +0.89$; $P < 0.0001$. Agreement was excellent (mean difference = -2.9 ± 16.1 mmHg). In 78% of all patients, agreement between EXAM and ECHO was within 15 mmHg and within 5 mmHg in 45%. Clinical estimates of PS PG were more accurate than of AS and VSD. A palpable precordial thrill and increasing loudness of the murmur predicted higher

gradients ($P < 0.0001$). Weight did not influence accuracy. A learning curve was evident, such that the most recent quartile of patients showed $ECHO = 1.01 (EXAM) + 1.9$, $r = +0.92$, $P < 0.0001$; during this time, the attending pediatric cardiologist had been > 10 years in practice.

CONCLUSION

Clinical examination can accurately estimate PG in PS, AS, or VSD. Continual correlation of clinical findings with echocardiography can lead to highly accurate diagnostic skills.

Key words: Physical examination; Ventricular septal defect; Clinical skills; Echocardiography; Aortic stenosis; Pulmonary stenosis

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Core tip: Knowing pressure gradients across valves, arteries, and ventricular septal defects is important to clinical management of patients. In a large cohort of patients, we have determined the high degree of accuracy of the physical examination against the benchmark Doppler echocardiography. We discuss this clinical approach in the context of clinical practice, technology, and healthcare costs.

Kadle RL, Phoon CKL. Estimating pressure gradients by auscultation: How technology (echocardiography) can help improve clinical skills. *World J Cardiol* 2017; 9(8): 693-701 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/693.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.693>

INTRODUCTION

Strong clinical skills, including history-taking and physical diagnostic skills, remain an important part of patient evaluation - central to the practice of medicine. The clinical skills required for auscultation are especially important in childhood, when more than 50% of children have heart murmurs, most of which are benign^[1,2]. In recent years however, there have been a decline in clinical examination skills and an increasing reliance on diagnostic testing^[3-7].

The gradual loss of emphasis on physical exam skills has several implications^[8-11]. The physical exam is an integral part of the doctor-patient relationship, and can also garner otherwise unattainable observations and findings. Additionally, the information obtained from the physical exam can help delineate the need for further testing. Although there have been several initiatives to minimize wasteful testing by focus on clinical examination^[12-14], few groups have described specific and learnable techniques to do so.

In this follow-up to a small pilot study^[15], our objectives of this study were several-fold. We hoped

to further validate our technique of estimating peak pressure gradients through auscultation with a much larger cohort of patients. We also hoped to debunk the idea that the physical exam has a dwindling role in medicine; we believe its use in conjunction with technology can allow for a more accurate clinical assessment. We also hoped to determine the specific situations and characteristics associated with a more accurate physical exam, allowing others to learn this technique as well.

MATERIALS AND METHODS

The methods are essentially as detailed in our previous report^[15]. This study was approved by the Institutional Review Boards at NYU Langone Medical Center and Bellevue Hospital Center (both located in New York, NY, United States). Including our initial cohort of 151 patients^[15], a total of 1193 consecutive patients with pulmonary stenosis (PS, $n = 563$), aortic stenosis (AS, $n = 234$), or ventricular septal defect (VSD, $n = 396$) were studied by both auscultation and Doppler echocardiography over a 13-year period between February 1997 and December 2009. Not all patients were diagnosed with these lesions at the visits; some were "first" visits, but the physical examination was characteristic for valvar stenosis or VSD, and therefore a clinical estimate of the pressure gradient could be made even before a diagnosis was established by echocardiography. All levels of PS (including tetralogy of Fallot) and AS, all types of VSDs, and residual lesions after surgical or transcatheter interventions were included. In our patient population, the AS seen was congenital, rheumatic, or postoperative, not the fibrocalcific AS seen in older patients. "Complex" AS or PS (as opposed to valvar AS or PS) denotes non-valvar stenosis, or multi-level stenosis; examples include the PS in patients with tetralogy of Fallot, subvalvular AS and supravalvular AS. It has been standard clinical practice in our pediatric echocardiography laboratory for the author (CKLP), an attending echocardiographer, to examine every patient briefly as time permits; it is felt by at least some echocardiographers, including the author, that this preliminary examination (which may include palpation and auscultation, especially of the heart sounds and murmurs) improves the reliability of the echocardiographic study. This physical examination helps to assess the degree of clinical suspicion and to focus the requested echocardiogram. For lesions with pressure gradients, the author routinely estimates a pressure gradient (see below) before the echocardiographic study. It should be noted this study was started (1997) only 1.5 years following the completion of clinical fellowship training by CKLP; therefore, at the completion of data acquisition (2009), 13.5 years had elapsed since completion of training.

The auscultatory pressure gradient was estimated by an "auscultatory scale" based predominantly on

Table 1 Summary table of key findings for pulmonary stenosis, aortic stenosis, and ventricular septal defect

Lesion	<i>n</i>	Mean gradient (mmHg)	Agreement to: ≤ 15 mmHg	≤ 10 mmHg	≤ 5 mmHg	<i>r</i>
Pulmonary stenosis						
PS (all)	563	42 ± 28	82%	70%	49%	0.85
Valvar PS	313	36 ± 22	89%	77%	56%	0.85
Complex PS	250	49 ± 32	72%	61%	40%	0.84
PVR	81	48 ± 25	84%	65%	42%	0.86
Aortic stenosis						
AS (all)	234	38 ± 24	81%	71%	49%	0.8
Valvar AS	112	42 ± 24	77%	68%	46%	0.76
Complex AS	122	34 ± 23	85%	75%	52%	0.85
AVR	34	46 ± 22	71%	65%	38%	0.71
Ventricular septal defect						
VSD	396	83 ± 31	70%	60%	36%	0.82

"Complex" AS or PS denotes non-valvar stenosis or multi-level stenosis, such as the PS observed in patients with tetralogy of Fallot. AS: Aortic stenosis; AVR: Aortic valve replacement; CHD: Congenital heart defects; PS: Pulmonary stenosis; PVR: Pulmonary valve replacement; VSD: Ventricular septal defect.

a murmur's perceived predominant frequencies and frequency spread^[15,16]. A stethoscope is inched around the chest until the highest frequencies of a murmur are heard. These frequencies are then used to estimate the pressure gradient. As the examiner continued to gain clinical experience, other components of auscultation were incorporated into the clinical estimate of the pressure gradients, including murmur loudness and length. Short murmurs generally comprised < 50% of systole, medium-length 50% to < 100% of systole with a crescendo-decrescendo quality, and long/holosystolic 100% of systole. Gradients were estimated in 5 mmHg range increments (for example, 5-10 mmHg or 25-30 mmHg) and then recorded as a midpoint value [5-10 (= 8 mmHg), 25-30 (= 28 mmHg), *etc.*]. In the remainder of this article, the terms "auscultation" and "auscultatory gradient" will refer to this technique of assessing the frequency composition of a murmur unless otherwise specified.

To avoid bias, the auscultatory gradient was recorded before Doppler echocardiography, and the Doppler examination was performed by a pediatric cardiac sonographer who was unaware of the auscultatory estimate. Echocardiograms performed solely by the author were excluded. In standard fashion, the Doppler beam was aligned as parallel as possible with the blood flow jet, without angle correction, interrogating for the maximal flow velocity from multiple views. The peak instantaneous Doppler pressure gradient was calculated with the modified Bernoulli equation. Any perceived inconsistencies between the auscultatory gradient and the echocardiographic results were resolved with further imaging.

Ideally, patients should be in a calm resting state for both the auscultatory examination and the echocardiogram because changes in activity level will change the cardiac output and therefore flow characteristics, including gradients. Because we do not routinely use conscious sedation, we examined patients in as calm a state as possible, recognizing that

variability in the resting state will introduce variability into our assessments.

Age, weight, diagnoses, and history of interventions were obtained from the patient reports.

The relationship between the auscultatory and Doppler pressure gradients was assessed by simple linear regression. Agreement was assessed by Bland-Altman analysis^[17]. Results are expressed as mean ± SD. Differences were analyzed with a 2-tailed Student *t* test. Comparison of categorical variables was performed with chi-square analysis or Fisher's exact test. Statistical significance was set at *P* < 0.05.

RESULTS

Patient demographics

Patients were 0-38.4 years old (mean 6.8 years, median 4.8), weighing 0.83-129 kg (mean 26.8 kg, median 18.2). There were 339 patients between 0-1 years of age (infants); 270 patients > 1 year-5 years (toddlers and young children); 311 patients between > 5 years-12 years (school-age children); 200 patients between 12-18 years (adolescents); and 73 patients older than 18 years (adults).

Accuracy and correlations of various congenital cardiac conditions

For all patients, auscultation correlated highly with echocardiography: ECHO= 0.99 (AUSC) + 3.2 mmHg; *r* = +0.89 (*r*² = +0.79); *P* < 0.0001 (Figure 1A). Agreement was excellent [mean difference between clinical exam and echo = -2.9 ± 16.1 mmHg (SD), also as seen in the Bland-Altman analysis, Figure 1B]. In 78% of all patients, agreement between auscultation and echocardiography was within 15 mm Hg; in 67%, within 10 mmHg; and in 45%, within 5 mmHg (Figure 1C). Clinical estimates of PS pressure gradients were more accurate than of AS and VSD (Table 1). Valvar PS appeared to be more accurately estimated than other lesions, and VSD showed the worst agreement overall.

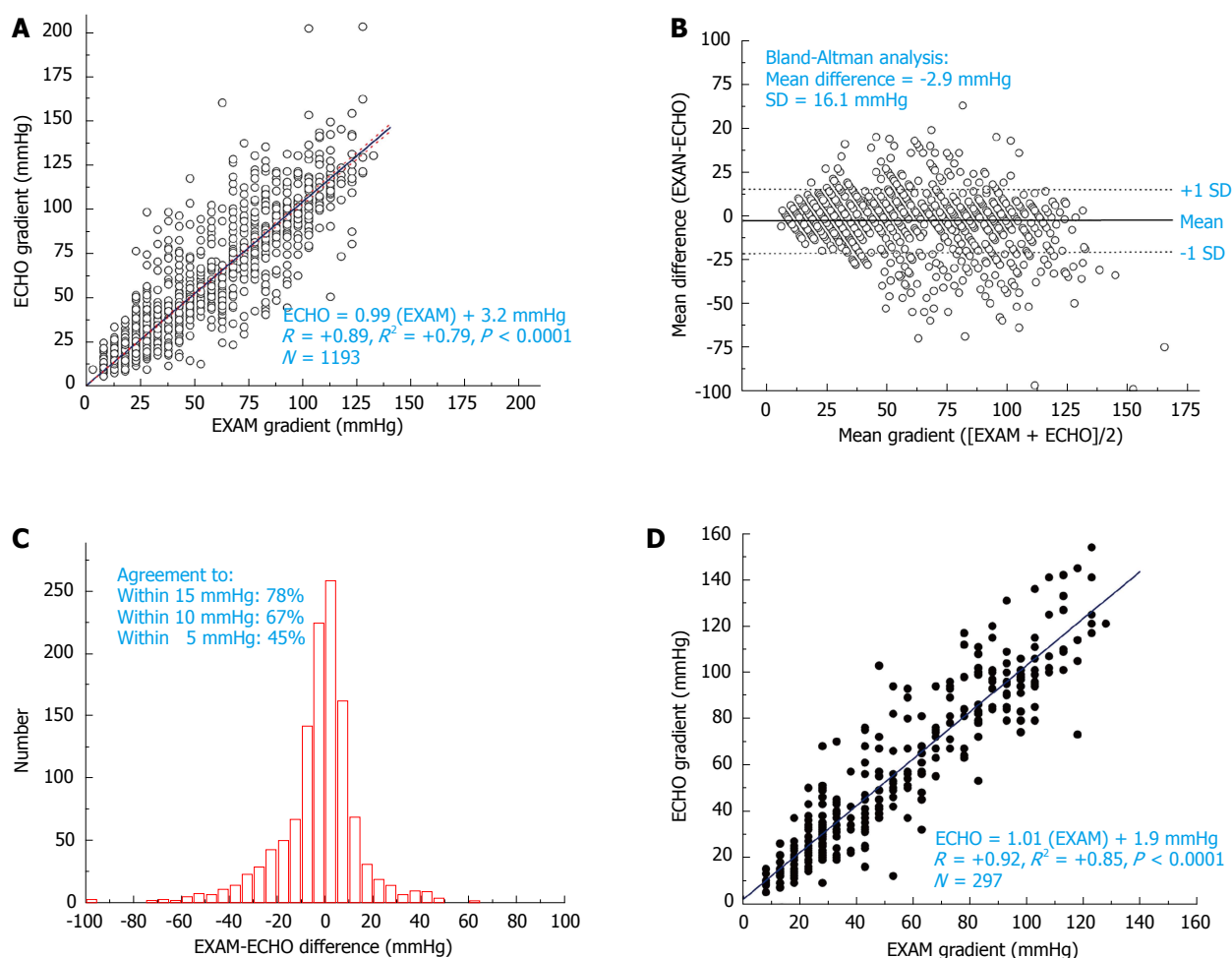


Figure 1 Accuracy and correlations of various congenital cardiac conditions. A: Regression plot of all patients; B: Bland-Altman plot; C: Histogram displaying spread between the Doppler and physical examination gradients, and the agreement between Doppler and physical examination to within 15, 10, and 5 mmHg; D: Regression plot of most recent quartile of patients.

A learning curve was evident. Overall agreement and correlation in the original published cohort of 151 patients [$ECHO = 0.99 (AUSC) + 7.12$, $r = +0.84$ ($r^2 = +0.71$)] were worse (Phoon 2001); the most recent quartile of patients showed $ECHO = 1.01 (AUSC) + 1.9$, $r = +0.92$ ($r^2 = +0.85$), $P < 0.0001$ ($n = 297$) (Figure 1D). The initial cohort^[15] corresponded to a time period from early 1997 through mid-1998, while the most recent quartile of data corresponded to a time period from mid-2007 through end of 2009; thus, there was a 10-year difference in clinical experience.

Correlates with patient factors affecting accuracy

Increasing loudness of the murmur (standard 1-6 grade scale) predicted higher gradients ($r = +0.54$, $P < 0.0001$), with the largest gap occurring between grades 2 (mean PG: $36 \pm 29 \text{ mmHg}$) and 3 (mean PG: $63 \pm 35 \text{ mmHg}$) (Figure 2A). Similarly and as expected, a palpable precordial thrill predicted significantly higher gradients [all $P < 0.0001$: PS: $32 \pm 22 \text{ mmHg}$ (no thrill) vs 67 ± 25 (+thrill); AS: 31 ± 20 vs 59 ± 29 ; VSD: 80 ± 31 vs 101 ± 28] (Figure 2B, C). Despite the highly significant differences in patients

with and without a palpable precordial thrill, there was considerable overlap in the pressure gradients. Possible influencing factors are shown in Table 2. Heavier weight and prior surgery did not appear to influence accuracy. Infants and young toddlers appeared to be less accurately assessed. Although a previous echocardiogram (and therefore possibly knowledge of the previous gradient) exhibited a better correlation, the correlation coefficient even during a “first” visit was very high (Table 2).

In several cases, the physical examination “trumped” the echocardiogram, although this represented a small percentage of all patients. Nearly all were VSD’s, for which Doppler echocardiography underestimated the predicted peak gradient due to a suboptimal Doppler incident angle (Table 3). In such cases, the VSD gradient alone would have predicted the presence of pulmonary hypertension.

DISCUSSION

This large dataset extends our previous observations and confirms that physical examination, relying mainly

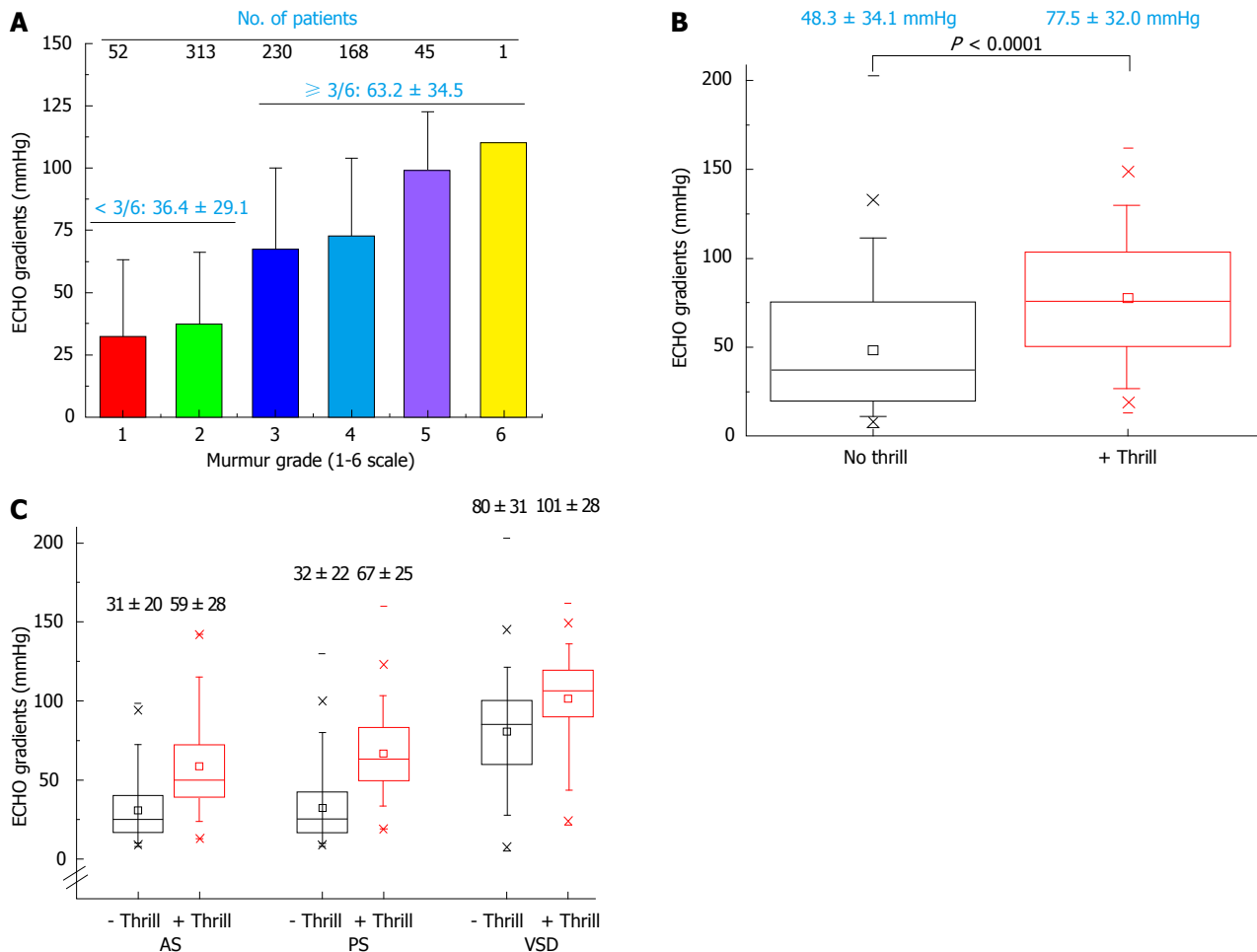


Figure 2 Correlates with patient factors affecting accuracy. A: Loudness of heart murmur (standard grade system, 1-6) plotted against peak Doppler ("ECHO") gradient; B: Box-and-whiskers plot of Doppler peak gradients in the absence and presence of a palpable thrill, all patients; C: Box-and-whiskers plots of specific congenital lesions (aortic stenosis, pulmonic stenosis, ventricular septal defect), thrill absent vs thrill present.

on auscultation, can be very accurate in determining pressure gradients. We emphasize that our purpose was not to diagnose specific conditions *de novo*, but to evaluate pressure gradients clinically. Other studies have previously demonstrated that the cardiac physical exam, specifically auscultation, can accurately distinguish benign from pathologic murmurs^[15,18-24]. Although these studies look at auscultation in general, they do not specifically analyze pressure gradients. We have now in more detail analyzed some of those aspects of clinical auscultation, as well as patient characteristics, which impact the accuracy of the physical examination. A key finding in this study is how technology - in this case, echocardiography - can help improve clinical skills, presumably by providing feedback to the examiner.

Comparison of different lesions: PS, AS, VSD

Pressure gradients have been examined in dogs, and have been found to both correlate with echocardiographic findings^[25-28] and be associated with severity of disease^[29]. These studies corroborate the validity of our findings, and we further show its applicability to human subjects. Several groups have

shown that examination can diagnose both AS and PS successfully^[30-36]. Diagnosis of VSDs by clinical exam is also accurate but can be imperfect for major VSDs^[37]. Our study takes these analyses further by laying out a specific auscultatory technique to assess heart murmurs, and by continually correlating clinical findings with echocardiographic data to improve accuracy. We demonstrate that auscultation has the greatest accuracy in predicting pressure gradients in PS, and is still accurate but less so in VSD. We speculate that the murmur of PS is consistently directed in a similar direction in nearly all patients, whereas VSD jets would exhibit far more variability that may change their auscultatory characteristics. We additionally experienced several cases in which echocardiography underestimated the severity of the murmur, or missed the etiology of a murmur completely, demonstrating the significance of auscultation in a clinical exam.

When to be careful: Accuracy is affected by certain patient variables

Several auscultatory characteristics have been identified to predict pathologic disease, such as holosystolic timing, harshness, grade 3 or more, or palpable

Table 2 Summary table of variables that might affect accuracy of clinical estimates of gradients

Variable	<i>n</i>	Mean gradient (mmHg)	Agreement to: ≤ 15 mmHg	≤ 10 mmHg	≤ 5 mmHg	<i>r</i>
Weight						
≤ 10 kg	367	61 ± 32	71%	61%	42%	+0.81
> 10 to 20 kg	270	57 ± 36	79%	69%	46%	+0.92
> 20 to 40 kg	236	53 ± 38	81%	71%	48%	+0.91
> 40 to 70 kg	237	49 ± 34	81%	67%	42%	+0.91
> 70 kg	82	45 ± 35	85%	74%	48%	+0.88
Age						
< 2 yr	414	60 ± 32	71%	62%	42%	+0.83
≥ 2 yr	779	52 ± 36	81%	70%	46%	+0.91
Prior echo?						
No prior	321	61 ± 36	72%	64%	43%	+0.85
+Prior	872	53 ± 35	79%	68%	45%	+0.90
Operative status (all CHD)						
No operative	688	65 ± 37	74%	64%	43%	+0.89
Post-operative	505	42 ± 27	82%	70%	46%	+0.87

CHD: Congenital heart defects.

Table 3 Examples of cases when physical examination “trumped” echocardiography or echocardiography presented misleading data

Case	Age (yr)	Lesion	Clinical Gradient	DOPP Gradient	Comment
1	6.7	Supravalvar PS s/p repair of TOF with homograft from RV to PA	63	24	Homograft poorly visualized; tricuspid regurgitation jet predicted a systolic RV pressure of 66 mmHg plus the right atrial v-wave, so the PS gradient was significantly underestimated by DOPP
2	6.9	VSD, s/p repair of TOF	70	66	Prior echocardiograms did not visualize VSD; exam led to finding of a tiny residual VSD
3	10.8	VSD	88	63	Poor DOPP incident angle predicted pulmonary hypertension
4	0.005	VSD	68	NA	VSD was so tiny and anterior, a jet could not be obtained for a DOPP gradient
5	4.3	VSD	73	61	BP 104/50; poor DOPP incident angle predicted pulmonary hypertension
6	0.01	VSD	88	48	Technician obtained initial VSD DOPP gradient of 28 mmHg; exam prompted a search for a better DOPP angle
7	2.8	VSD	83	55	Poor DOPP incident angle predicted pulmonary hypertension; tricuspid regurgitation jet predicted normal PA pressures
8	5.5	VSD, s/p repair	98	62	Poor DOPP incident angle predicted pulmonary hypertension; tricuspid and pulmonary regurgitation jets predicted normal PA pressures
9	3.8	VSD	73	53	Poor DOPP incident angle predicted pulmonary hypertension; tricuspid regurgitation jet predicted normal PA pressures
10	15.4	VSD, Shone's complex with minimal LV outflow tract obstruction	93	63	Poor DOPP incident angle predicted pulmonary hypertension
11	15.7	VSD	118	73	Poor DOPP incident angle predicted pulmonary hypertension, even though the VSD was 2.8 mm in diameter; tricuspid and pulmonary regurgitation jets predicted normal PA pressures

BP: Blood pressure; DOPP: Doppler echocardiography; LV: Left ventricular; PA: Pulmonary artery; PS: Pulmonary stenosis; RV: Right ventricular; TOF: Tetralogy of Fallot; VSD: Ventricular septal defect.

precordial thrill^[24,38]. We confirmed such factors can be used to estimate pressure gradients clinically, specifically the loudness of the murmur and the presence of a palpable thrill. Somewhat surprisingly, neither heavier weight nor prior surgery worsened clinical accuracy, even though we had wondered if adipose or scar tissue would impact the auscultated frequency spectrum of heart murmurs.

We believe several teaching points can be made from our data. Although the data exhibit much overlap, the presence of a precordial thrill may help differentiate higher gradients in PS and AS, although this appears to be much less useful with VSD's. For both PS and AS,

the presence of a thrill is likely to indicate a pressure gradient of > 40–45 mmHg. Infants and toddlers also are more difficult to assess clinically.

Philosophical and practical issues

Our study raises the question of whether clinical skills such as these are important in the current era of medical practice. It is debatable or even unlikely a study such as this will impact use of technology or healthcare costs significantly. Nevertheless, it is our impression that: (1) some cases were diagnosed based primarily on clinical findings, and echocardiography played a limited or initially misleading role; and (2)

our data exposes some strengths and weaknesses of the cardiac physical examination with regards to estimating pressure gradients. We and others continue to believe the gradual loss of emphasis on physical exam skills has several implications.

The physical exam is a central part of the doctor-patient relationship. The intimate contact of a physical exam not only gives the patient a sense of comfort and confidence in their physician, but can itself help the patient heal^[10,11,39,40]. Besides the desired dynamic bedside skills help to create, there is also a great deal of information obtained through the physical exam that might otherwise be lost^[11,41]. Many clinical signs and symptoms cannot be classified by technology alone, and can only be appreciated with a thorough physical exam. Fred discussed the implications of over-reliance on CT scans in the diagnosis of patients, including delays in treatment by waiting for a CT scan to confirm a diagnosis that can be made by physical examination alone^[9]. McGee described several instances where the physical exam bested technological testing, including reactive arthritis and pericarditis^[42].

However, as Verghese *et al.*^[39] argue, it is not a fight of physical exam skills vs technology, but the attempt to merge these two to produce the optimal comprehensive exam. Ippisch *et al.*^[43] demonstrated this with regards to cardiology specifically. Neither the physical exam nor a hand-carried echocardiography machine were as accurate as the two used together^[6]. We conclude that technology does not erode physical exam skills but in fact improves both bedside skills and clinical judgment. Technology and clinical examination can and should go hand-in-hand for optimal patient care. "It has to make sense"^[16].

Balancing exam with technology

Recently, several groups have discussed the development of technologies that can assist physicians in analyzing heart murmurs, including computer-assisted auscultation and artificial neural networks^[44,45]. Heart murmurs are complex sounds that can nevertheless be analyzed by a simple frequency analysis, which can be done either with advanced technologies or with a trained ear and a stethoscope.

It has been shown that physicians listening to recorded heart sounds can accurately distinguish innocent from pathologic murmurs^[46-48]. Therefore, telecardiology (tele-auscultation) may find potential use in areas where access to echocardiography is limited. Many rural areas, both in the United States and around the world, do not have either an echocardiography machine or a trained echocardiographer. Doctors trained to auscultate for peak pressures could feasibly receive digital heart sounds from remote areas, and improve remote diagnostic capabilities.

Cost considerations

As physicians move away from their stethoscopes,

they increasingly rely on diagnostic testing that may be unnecessary and is often uninformed, and certainly costly. Unfortunately in our study, it is impossible to know how many patients could have avoided an echocardiogram, based purely on auscultatory estimation of a pressure gradient; other clinical questions may also prompt an echocardiogram. Nevertheless, in response to the increasing impact of echocardiography on health care costs, the ACCF and the ASE prepared a 2011 revision on appropriate use criteria (AUC) for echocardiography^[14]. More recently AUC has also been described for pediatric echocardiography, specifically to determine the need for TTE as an initial diagnostic tool in the outpatient setting^[13]. The AUC are not absolute, but should be applied to clinical exams to determine when an echocardiogram is appropriate. We believe that an increased focus on auscultation would aid in this.

Limitations

This technique has been proven rigorously for one cardiologist only. The study period corresponded to this cardiologist's early and middle career. Of note, in our original study, we validated the auscultatory scale using a senior pediatric cardiology fellow. In our anecdotal experience, several other individuals have mastered this technique to some degree. Similar to our findings, others have shown that attention to clinical examination skills can allow residents and students to improve their physical exam skills and diagnoses^[1]. Moreover, similar findings in animal studies as cited above further validate our approach^[25-29].

This study was performed primarily in children but included heavier children as well as some adults. Still, this data may not be applicable to adults with calcific valve disease or other pathologies not addressed in this study. In addition, pressure gradients depend on flow, and the true severity of a valvar or arterial obstruction may not be reliably assessed when there is myocardial failure. For instance, severe AS in adults may present with only a short, unimpressive midsystolic murmur or even no murmur at all. Finally, we did not test this technique for diastolic gradients.

Conclusions and future directions

Physical examination can accurately estimate pressure gradients in most patients with PS, AS, or VSD. An accurate physical examination may provide data that may be missed by technology, contribute to the patient-doctor relationship, and has a role for the cost-conscious physician. And it may prove useful in areas with limited access to technological resources. We do not propose that the physical exam should replace echocardiography, but believe that the use of the two in conjunction allows for the optimal patient assessment. Contrary to the belief that technology erodes clinical skills, continual correlation of clinical findings with a technological "gold standard" such as echocardiography can lead to highly accurate

diagnostic skills and improved clinical judgment, thereby enhancing clinical skills training and further substantiating the value of clinical examination.

COMMENTS

Background

Strong clinical skills, including physical examination skills, remain central to the practice of medicine. In recent years, there has been a much-decried decline in clinical examination skills. The authors had performed a small pilot study over 15 years ago with 151 patients that indicated that physical examination can be very accurate in determining pressure gradients across stenosis or septal defects.

Research frontiers

Very little research is being performed to help clinicians improve clinical skills, or to determine the strengths and/or weaknesses of clinical examination. Moreover, very little is known about how technology such as imaging can help clinicians improve their physical examination skills.

Innovations and breakthroughs

In pediatric cardiology, physical examination is felt to be very accurate in determining normal from abnormal heart murmurs. What is not known, however, is whether the physical examination can accurately predict pressure gradients in aortic stenosis, pulmonary stenosis, and ventricular septal defect. Knowledge of such pressure gradients helps guide clinical management. Almost no work has been done on this area.

Applications

Honing physical examination skills such as being able to predict pressure gradients has two potential benefits: (1) The clinician may rely less on technology and therefore may reduce the use of expensive testing (imaging); and (2) The clinician may use the physical examination findings in conjunction with testing (imaging) to come to a better overall evaluation of the patient.

Terminology

Aortic stenosis (AS): Anatomical obstruction to blood flow at any level, including subaortic stenosis, valvar aortic stenosis, supra-aortic stenosis (narrowing of the ascending aorta). In this project, aortic stenosis did not include coarctation of the aorta; Pulmonary stenosis (PS): Anatomical obstruction to blood flow at any level, including subpulmonary or infundibular stenosis, valvar stenosis, and supra-aortic stenosis (narrowing of the main pulmonary artery). For the purposes of this project, the authors did not include stenoses of the peripheral branch pulmonary arteries; Ventricular septal defect (VSD): the authors included VSD's at any site, including perimembranous, muscular, and supracristal (subpulmonary) VSD's; Doppler echocardiography, peak instantaneous pressure gradient: For aortic or pulmonary stenosis, there will be a higher-pressure site (proximal to the obstruction) and a lower-pressure site (distal to the obstruction). For ventricular septal defects, the higher-pressure site is generally the left ventricle, while the lower-pressure site is the right ventricle. The difference in pressures (ΔP) between the two sites in the heart or arteries can be estimated using the Doppler principle on echocardiography systems; most commonly, one uses the modified Bernoulli equation, $\Delta P = 4V^2$, where V is the maximal velocity across the region of interest (stenosis or VSD) as acquired from the Doppler ultrasound transducer.

Peer-review

This is a well-written and interesting paper demonstrating how clinical auscultation in expert hands may approximate echo results. The results are important in an era of considerable expenses in technology and of looking down on clinical examination.

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Observational Study

Coronary angiography findings in cardiac arrest patients with non-diagnostic post-resuscitation electrocardiogram: A comparison of shockable and non-shockable initial rhythms

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Informed consent statement: All patients' relatives signed informed consents for the clinical procedures performed during admission. No special tests were done for this study. Therefore, no specific informed consent was obtained for this anonymous observational study.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: Technical details and statistical methods are available from the corresponding author at salinas.pablo@gmail.com.

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Abstract

AIM

To investigate the impact of coronary artery disease in a cohort of patients resuscitated from cardiac arrest with non-diagnostic electrocardiogram.

METHODS

From March 2004 to February 2016, 203 consecutive patients resuscitated from in or out-of-hospital sudden cardiac arrest and non-diagnostic post-resuscitation electrocardiogram (defined as ST segment elevation or pre-sumably new left bundle branch block) who

underwent invasive coronary angiogram during hospitalization were included. For purpose of analysis and comparison, patients were classified in two groups: Initial shockable rhythm (ventricular tachycardia or ventricular fibrillation; $n = 148$, 72.9%) and initial non-shockable rhythm ($n = 55$, 27.1%). Baseline characteristics, coronary angiogram findings including Syntax Score and long-term survival rates were compared.

RESULTS

Sudden cardiac arrest was witnessed in 95.2% of cases, 66.7% were out-of-hospital patients and 72.4% were male. There were no significant differences in baseline characteristics between groups except for higher mean age (68.1 years vs 61 years, $P = 0.001$) in the non-shockable rhythm group. Overall 5-year mortality of the resuscitated patients was 37.4%. Patients with non-shockable rhythms had higher mortality (60% vs 29.1%, $P < 0.001$) and a worst neurological status at hospital discharge based on cerebral performance category score (CPC 1-2: 32.7% vs 53.4%, $P = 0.02$). Although there were no significant differences in global burden of coronary artery disease defined by Syntax Score (mean Syntax Score: 10.2 vs 10.3, $P = 0.96$) there was a trend towards a higher incidence of acute coronary lesions in patients with shockable rhythm (29.7% vs 16.4%, $P = 0.054$). There was also a higher need for *ad-hoc* percutaneous coronary intervention in this group (21.9% vs 9.1%, $P = 0.03$).

CONCLUSION

Initial shockable group of patients had a trend towards higher incidence of acute coronary lesions and higher need of *ad-hoc* percutaneous intervention vs non-shockable group.

Key words: Sudden cardiac arrest; Electrocardiogram; Invasive coronary angiography; Percutaneous coronary intervention; Syntax score; Coronary artery disease

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Core tip: Coronary artery disease represents the most common cause of sudden cardiac arrest. Current resuscitation guidelines recommend emergency coronary angiography in patients with cardiac arrest and ST elevation or new left bundle branch block on post-resuscitation electrocardiogram. However, electrocardiogram findings may be a poor predictor of an acute coronary lesion in this context and nowadays, the benefit of early coronary angiography is still under debate in patients without ST elevation. In this study, we analyzed our single-center data of patients with cardiac arrest and non-diagnostic electrocardiogram to describe the burden of coronary artery disease and their prognosis depending on initial rhythm.

Noriega F, Del Trigo M, Núñez-Gil JJ, Nombela-Franco L, Gonzalo N, Jiménez-Quevedo P, Escaned J, Fernández-Ortiz A, Macaya C, Viana-Tejedor A. Coronary angiography findings in cardiac arrest patients with non-diagnostic post-resuscitation electrocardiogram: A comparison of shockable and non-shockable initial rhythms. *World J Cardiol* 2017; 9(8): 702-709 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/702.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.702>

INTRODUCTION

Sudden cardiac arrest (SCA) is one of the most common causes of death in the developed world, affecting nearly 560000 people annually in the United States. Although a majority of deaths occur during the initial resuscitation, a substantial proportion of cardiac arrest deaths occur in patients who have been initially successfully resuscitated after first medical contact. Despite the important advances in emergency medical services and post cardiac arrest syndrome care over the last decades, survival free from neurological deficit is still low^[1].

Coronary artery disease (CAD) represents the most common cause of SCA and current resuscitation guidelines recommend the performance of an emergency coronary angiography (CA) and appropriate percutaneous coronary interventions (PCI) in patients with SCA and ST segment elevation or presumably new left bundle branch block (LBBB) on post-resuscitation electrocardiogram (ECG). In patients without ST elevation after SCA but with suspected or with a high risk of cardiac origin, emergency CA is reasonable in selected situations (for example, electrically or hemodynamically unstable patients)^[2,3]. Such "suspicion of cardiac origin" is not well defined and therefore the recommendation remains somewhat ambiguous.

Regarding the likelihood of a cardiac origin of the SCA, the ECG may be a poor predictor of acute coronary occlusion in resuscitated patients^[4-7]. Also, a recent meta-analysis showed a high prevalence of significant CAD ranging from 59% to 71% in patients resuscitated from SCA without an obvious non-cardiac etiology^[8]. Furthermore, pre-arrest symptoms reported in this setting are unreliable and dependent on the presence of by-standers. In summary, the suspicion of cardiac origin is largely subjective or uncertain for most patients. For these reasons, and without available randomized data, the justification for use of an early invasive strategy in survivors of SCA without an obvious non-cardiac cause of arrest is based on observational data^[9-11].

From a single-center registry of patients resuscitated from SCA undergoing CA, we present in this paper the results of a sub-analysis comparing patients with shockable and non-shockable initial rhythms^[12]. The aim of this sub-analysis was to investigate the impact of CAD in a cohort of SCA patients with non-diagnostic

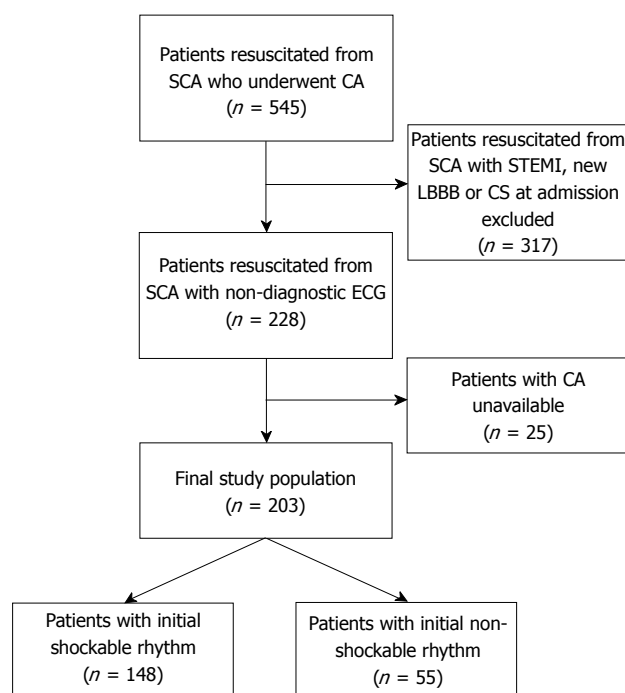


Figure 1 Patient flowchart. CA: Coronary angiography; CS: Cardiogenic shock; ECG: Electrocardiogram; LBBB: Left bundle branch block; SCA: Sudden cardiac arrest.

ECG depending on initial rhythm.

MATERIALS AND METHODS

Study population

All patients recovered from in or out-of-hospital SCA and admitted to a tertiary care center with 24/7 emergent PCI availability that underwent invasive CA were extracted from a multipurpose database including data from interventional procedures, critical care unit and hospital admission.

From March 2004 to February 2016, 545 consecutive SCA patients were identified. For this study, we focused on patients without emergent indication for CA. Therefore, patients with ST segment elevation or presumably new LBBB on post-resuscitation ECG, or cardiogenic shock at admission were excluded ($n = 317$). Of the remaining 228 patients, 25 had unavailable or incomplete CA films. Thus, our final study population was 203 patients. For the purpose of this sub-analysis, patients were classified into two groups depending on initial ECG: Shockable [ventricular tachycardia or ventricular fibrillation ($n = 148$, 72.9%)] and non-shockable rhythm ($n = 55$, 27.1%) (Figure 1).

Clinical and outcome data were collected from clinical record, patient's charts or telephone contact with patients or their relatives. Follow-up was completed up to 5-year after index admission.

Cardiac catheterization

The indication and timing of CA in our study population was individualized for each patient based on treating

physician's criterion. CA was classified as early when performed < 24 h after hospital admission or late when performed ≥ 24 h after admission. Two interventional cardiologist reviewed all CA blinded to original reports. The percentage diameter stenosis (DS%) was visually estimated for each lesion. Quantitative CA was used if discordances $> 10\%$ were found between both investigators. Significant stenosis was defined as ≥ 50 DS%, severe stenosis when DS% was $\geq 70\%$ and non-obstructive CAD when DS% was $< 50\%$. A normal coronary angiogram was defined as 0 DS% in all arteries with no other pathological findings. Culprit lesion was defined as the presence of an acute arterial occlusion (plaque rupture with occlusive thrombus) or an incomplete coronary artery occlusion in presence of complex lesion morphology as previously defined^[13]. Chronic total occlusion (CTO) was defined as a Thrombolysis In Myocardial Infarction (TIMI) grade 0 flow for at least 3 mo of estimated duration. Estimation of occlusion duration was based on at least one of the following: Prior history of myocardial infarction in the target vessel territory, comparison with a previous angiogram, or the presence of collateral circulation or bridging collaterals. Critical stenosis was considered when DS% was $\geq 90\%$ but $< 100\%$ and there were no CTO features. Acute coronary lesion was defined as critical or culprit lesion for the purpose of this investigation. *Ad-hoc* PCI was defined if performed at the moment of the index CA at the operator's discretion. Procedural success was defined as complete restoration of antegrade blood flow (TIMI 3) and $< 30\%$ residual diameter stenosis by visual assessment.

Burden of CAD was measured using the Synergy Between Percutaneous Coronary Intervention With Taxus And Cardiac Surgery (SYNTAX) Score and number of vessels with significant and/or severe stenosis. We calculated the Syntax Score for each patient, as previously reported^[14,15]. If the patient had previous PCI we used residual Syntax score (rSS) defined as the SYNTAX score remaining after PCI. If the patient had previous coronary artery bypass graft (CABG) surgery we calculated the CABG-SYNTAX score proposed by Farooq *et al.*^[16]. Both rSS and CABG-SYNTAX score reflect the current burden of CAD (successfully revascularized segments are equalized to segments with CAD $< 50\%$, thus not incrementing SYNTAX score).

Statistical analysis

Statistical analysis was performed using SPSS 21 (SPSS Inc, Illinois, Chicago, United States). Continuous variables are presented as mean and standard deviation. Categorical variables are expressed as frequency and percentage. In quantitative variables, the groups were compared using a two-tailed Student's *t*-test for independent samples. Categorical variables were compared with the χ^2 test. The Kaplan-Meier method was used to estimate the cumulative patient survival rates and log-rank test for comparison. All test were two

Table 1 Baseline characteristics of study patients *n* (%)

	All patients (<i>n</i> = 203)	Non-shockable rhythm (<i>n</i> = 55)	Shockable rhythm (<i>n</i> = 148)	<i>P</i> value
Age (mean ± SD)	62.9 ± 14	68.1 ± 13	61 ± 13.9	0.001
Male sex	147 (72.4)	36 (65.5)	111 (75)	0.176
Arterial hypertension	123 (60.6)	37 (67.3)	86 (58.1)	0.235
Diabetes mellitus	65 (32)	22 (40)	43 (29.1)	0.137
Dyslipidemia	80 (39.4)	26 (47.3)	54 (36.5)	0.162
Smoking	103 (50.7)	27 (49.1)	76 (51.4)	0.775
Peripheral vascular disease	23 (11.3)	7 (12.7)	16 (10.8)	0.702
Cerebrovascular disease	18 (8.9)	6 (10.9)	12 (8.1)	0.533
Prior MI	45 (22.2)	14 (25.5)	31 (20.9)	0.780
Prior PCI	35 (17.2)	10 (18.2)	25 (16.9)	0.829
Prior CABG	22 (10.8)	7 (12.7)	15 (10.1)	0.597
Out-of-hospital SCA	124 (66.7)	30 (58.8)	94 (69.6)	0.163
Time to ROSC	17.8 ± 12.7	14.8 ± 11.9	19 ± 12.9	0.122
Witnessed arrest	157 (95.2)	40 (93)	117 (95.9)	0.450
Coma status at admission	148 (84.6)	40 (88.9)	108 (83.1)	0.352
Cardiogenic shock	48 (23.6)	18 (32.7)	30 (20.3)	0.063
Therapeutic hypothermia	71 (41.8)	14 (32.6)	57 (44.9)	0.402

Values are given as mean ± SD or *n* (%). MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; SCA: Sudden cardiac arrest; ROSC: Return of spontaneous circulation.

Table 2 Angiographic characteristics *n* (%)

	All patients (<i>n</i> = 203)	Non-shockable rhythm (<i>n</i> = 55)	Shockable rhythm (<i>n</i> = 148)	<i>P</i> value
Normal coronaries	71 (35)	20 (36.4)	51 (34.5)	0.800
Mean Syntax Score	10.3 ± 12.4	10.2 ± 13.6	10.3 ± 11.9	0.961
Any vessel with significant stenosis (DS ≥ 50%)	125 (61.6)	33 (60)	92 (62.2)	0.778
Significant stenosis				
None	79 (38.9)	22 (40)	57 (38.5)	0.710
One vessel	46 (22.7)	15 (27.3)	31 (20.9)	
Two vessels	40 (19.7)	9 (16.4)	31 (20.9)	
Three vessels	38 (18.7)	9 (16.4)	29 (19.6)	
Any vessel with severe stenosis (DS ≥ 70%)	111 (54.7)	28 (50.9)	83 (56.1)	0.480
Any CTO	60 (29.6)	14 (25.5)	46 (31.1)	0.388
Critical stenosis	51 (25.1)	9 (16.4)	42 (28.4)	0.079
Culprit lesion	25 (12.3)	4 (7.3)	21 (14.2)	0.173
Acute lesion	53 (26.1)	9 (16.4)	44 (29.7)	0.054
<i>Ad hoc</i> PCI	37 (18.2)	5 (9.1)	32 (21.6)	0.036

Values are given as mean ± SD or *n* (%). CTO: Chronic total occlusion; DS%: Percentage diameter stenosis; PCI: Percutaneous coronary intervention.

sided and $P < 0.05$ was considered significant.

RESULTS

Baseline characteristics

Of 203 consecutive patients resuscitated from SCA with non-diagnostic ECG, 148 had initial shockable rhythm and 55 had non-shockable rhythm. Table 1 shows the baseline characteristics of the study cohort. There were no statistical differences between groups in baseline characteristics except for higher mean age in the initial non-shockable group (68.1 years vs 61 years, $P = 0.001$).

CA findings

Early CA was performed in 115 patients (56.9%). The most relevant angiography findings are reproduced in Table 2. Overall, mean value of Syntax Score

calculated was 10.30 with no statistical differences between groups (10.33 vs 10.23, $P = 0.95$). There were also no differences ($P = 0.71$) in the percentage of vessels with significant stenosis (0, 1, 2 or 3 vessels with ≥ 50 DS%). However, patients with initial shockable rhythm showed a trend towards a higher incidence of acute coronary lesions (29.7% vs 16.4%, $P = 0.054$) and higher rate of *ad-hoc* PCI (21.9% vs 9.1%, $P = 0.03$), mainly for left anterior descending artery lesions (45.9%).

The prognostic value of acute coronary lesions as defined by this study was assessed through a stratified Kaplan Meier analysis. Figure 2 shows Kaplan Meier curves for all cause 5-year survival depending on the finding of an acute coronary lesion. Patients with shockable rhythm and with acute coronary lesions had a non-significant increased mortality, whereas no significant differences or trends were found in the

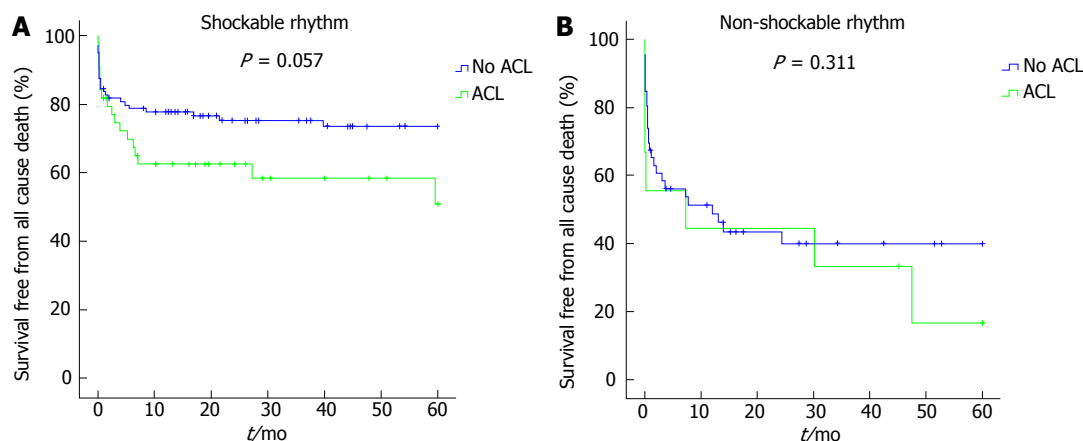


Figure 2 Kaplan Meier curves for all cause 5-year survival depending on the finding of an acute coronary lesion. ACL: Acute coronary lesion.

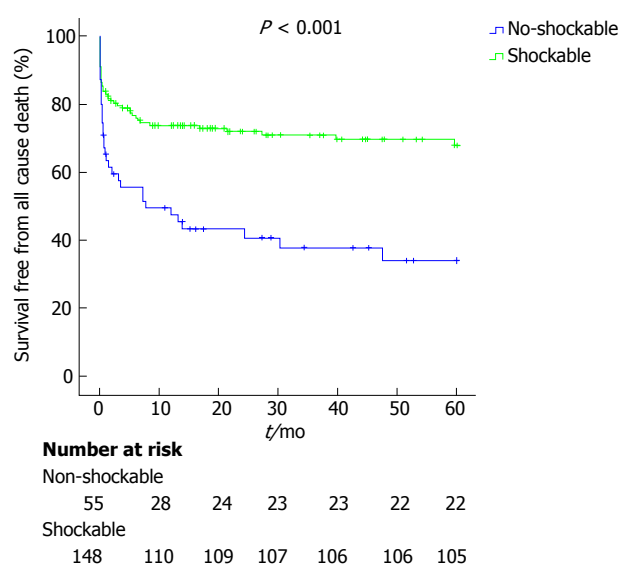


Figure 3 Kaplan-Meier curves for 5 years survival.

non-shockable group. Interestingly, in patients with shockable rhythm, those who underwent *ad hoc* PCI of the acute coronary lesions had a trend towards improved survival compared to patients with untreated acute coronary lesions (mean all-cause survival 41.3 ± 5.4 mo vs 29.7 ± 6.9 mo, $P = 0.147$). However, in patients with initial non-shockable rhythm, *ad hoc* PCI did not improve survival rates ($P = 0.948$).

In-hospital and long-term survival

Overall, 151 (74.4%) patients survived until hospital discharge and 97 (64.2%) survived with a favorable neurological outcome based on cerebral performance category score (CPC). Patients with initial shockable rhythm had a better prognosis, with higher survival rates to discharge compared with those with non-shockable rhythm (56.4% vs 81.1%, $P < 0.001$). Patients with shockable rhythm also had a better neurological status at discharge (CPC 1-2: 32.7% vs 53.4%, $P = 0.02$). Five-years mortality was 37.4% in the global cohort. Patients with non-shockable rhythm

had a higher five-year mortality (60% vs 29.1%, $P < 0.001$, Figure 3).

DISCUSSION

This study is a sub-analysis of a large single-center registry of selected SCA patients with CA and non-diagnostic post resuscitation ECG^[12]. The present study compares shockable vs non-shockable rhythms and reveals a similar high burden of CAD in both groups. Although these findings are consistent with previous observational studies^[8], our study is novel because it is the first to explore differences between shockable and non-shockable rhythms in this setting. Since the publication in 1997 of a seminal study by Spaulding *et al*^[17], many studies with important methodological limitations have reported the possible survival impact of an early invasive approach in this context^[9,18-21]. However, other studies did not find any benefit from such an invasive strategy and proposed to restrict its use to highly selected patients^[10,11,22]. Besides, in contrast to the usual presentation of acute coronary syndromes, the standard tools to evaluate coronary ischemia in post cardiac arrest patients are less accurate. The sensitivity and specificity of the usual clinical data, ECG or biomarkers to predict an acute coronary artery occlusion are unclear^[4-6,23]. For these reasons, there is still an ongoing debate on the use of an early invasive strategy in all survivors of SCA without an obvious non-cardiac cause. We conducted this sub-analysis in order to assess if the initial rhythm after resuscitation could be a predictor of CAD burden and acute coronary lesions.

Given the high probability of CAD (measured as mean Syntax Score), our data supports a low threshold for CA regardless of initial rhythm. According to current resuscitation guidelines, it is reasonable to discuss and consider emergent cardiac catheterization in patients with a high risk of a coronary cause for their cardiac arrest^[3]. However, definitive data will come with the results of several ongoing randomized trials designed to determine whether early CA improves outcomes in

out-of-hospital cardiac arrest, in patients without ST elevation [one of those (COUPE trial) conducted by our group]^[24-27].

Some differences in acute coronary lesions were found between the two groups. Those patients with initial shockable rhythm had a higher incidence of acute coronary lesions (29.7% vs 16.4%, $P = 0.054$) and consequently a greater requirement of *ad-hoc* PCI (21.9% vs 9.1%, $P = 0.03$). These acute coronary lesions might also have a potential impact on prognosis (Figure 2). Unfortunately, our study was underpowered to show the effect of revascularization on these lesions, but this should be considered a relevant research target for future studies. These findings are in accordance with the observed trend that reveals that CA and PCI after ventricular tachycardia or ventricular fibrillation has substantially increased over the last years, regardless of the presence of ST elevation^[28].

Regarding the prognosis of initial ECG rhythm analysis, SCA patients are usually divided into non-shockable rhythms (pulseless electrical activity and asystole) or shockable rhythms (ventricular tachycardia and ventricular fibrillation). Non-shockable rhythms are the most prevalent first recorder rhythm and survival rates of this group are worst compared with initial shockable rhythm^[1]. Studies have shown that increased age, female gender, and prolonged ROSC are associated with a non-shockable rhythm while public location and witnessed arrest are associated with a shockable rhythm^[29]. In our study, survival rates were also higher in patients with initial shockable rhythms (60% vs 29.1%, $P < 0.001$), as previously reported^[1]. However, there were no statistical differences in baseline characteristic except for higher mean age (68.1 years vs 61 years, $P = 0.001$) in the non-shockable rhythm group, probably due to the study design and patients selection.

The present study should be interpreted within the context of several limitations of a single-center observational study and relatively small size of the study population. The cohort included in this study was selected from consecutive patients who survived to in or out-of-hospital SCA and were subsequently selected for CA by clinicians upon admission. Patients with an explicit non-cardiac etiology of SCA would not be selected for CA and the final decision to proceed with CA was based on the clinical judgment of individual physicians. It is likely that CA was selectively more frequently offered to patients with a better likelihood of neurological recovery.

In conclusion, in our cohort of patients with SCA and non-diagnostic ECG, initial shockable rhythm group of patients had a similar burden of CAD compared to those with non-shockable rhythms. Patients with initial shockable rhythm had a trend towards a higher incidence of acute coronary lesions and a higher need of *ad-hoc* percutaneous coronary intervention. A low threshold for early CA should be considered in this subgroup of resuscitated SCA patients.

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COMMENTS

Background

Acute coronary syndromes are a common cause of sudden cardiac arrest (SCA). Based on observational studies, current resuscitation guidelines recommend emergency coronary angiography (CA) in patients with SCA and ST segment elevation on post-resuscitation electrocardiogram (Class I, level B). However, because of fewer data available, in patients without ST segment elevation, emergency CA is reasonable in selected patients with suspected cardiac origin (Class II a, level C), regardless of initial rhythm.

Research frontiers

Electrocardiogram findings may be a poor predictor of an acute coronary lesion in patients after a SCA. Without randomized data, the benefit of early CA in patients without ST elevation remains controversial.

Innovations and breakthroughs

In patients with SCA and non-diagnostic post-resuscitation electrocardiogram, initial shockable rhythms show a trend towards a higher incidence of acute coronary lesions and higher need of *ad-hoc* percutaneous coronary intervention.

Applications

The results of the study suggest that a low threshold for early CA should be considered in this subgroup of resuscitated SCA patients.

Terminology

Shockable rhythms include ventricular tachycardia and ventricular fibrillation in opposition to non-shockable rhythm that include asystole and pulseless electrical activity.

Peer-review

The manuscript is well-written, the statistical analysis is appropriate, and the data support the conclusions. This work will be of interest to the readership, and is potentially impactful regarding acute treatment of initially resuscitated, hospitalized cardiac arrest patients.

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Very late bioresorbable scaffold thrombosis and reoccurrence of dissection two years later chronic total occlusion recanalization of the left anterior descending artery

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Abstract

We describe the case of a patient presenting with ST-segment elevation myocardial infarction due to very late scaffold thrombosis. The patient was already admitted for an elective percutaneous recanalization of a chronically occluded left anterior descending artery (LAD). The procedure was performed according the sub-intimal tracking and re-entry (STAR) technique with 4 bioresorbable vascular scaffolds implantation. However, even though the coronary flow was preserved at the end of the procedure, the dissected segment was only partially sealed at the distal segment of the LAD. After 18 mo of regular assumption, dual antiplatelet therapy was discontinued for 10 mo before his presentation at the emergency room. This is the first reported case of a very late scaffold thrombosis after coronary chronic total occlusion (CTO) recanalization performed according to the STAR technique. This case raises concerns about the risk of very late scaffold thrombosis after complex CTO revascularization.

Key words: Bioresorbable vascular scaffolds; Scaffold dismantling; Scaffold thrombosis

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Core tip: We describe a case of a 53-year-old male patient who was admitted with anterior ST-elevation myocardial infarction 28 mo after elective percutaneous revascularization of a chronically occluded left anterior descending (LAD) threatened with 4 bioresorbable vascular scaffolds (BVS) in order to seal a long flow limiting dissection after sub-intimal tracking and re-entry technique. Coronary angiography showed a large thrombus at the proximal segment of the proximal BVS and a long dissection was evident from mid to distal LAD. In this case, the progressive reduction of both scaffolds radial strength and structure dismantling might have been responsible for both intraluminal thrombosis and reoccurrence of vessel dissection.

Di Serafino L, Cirillo P, Niglio T, Borgia F, Trimarco B, Esposito G, Stabile E. Very late bioresorbable scaffold thrombosis and reoccurrence of dissection two years later chronic total occlusion recanalization of the left anterior descending artery. *World J Cardiol* 2017; 9(8): 710-714 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i8/710.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i8.710>

INTRODUCTION

Bioresorbable vascular scaffolds (BVS) represents the latest revolution in the field of interventional cardiology. Providing temporary scaffolding and disappearing few years later, BVS results particularly appealing for the treatment of long segments of coronary arteries such as it usually occurs for percutaneous revascularization (PCI) of chronic total occlusions (CTO). However, limited data are available about the long-term efficacy of BVS in this particular setting. Herein we report a case of a very late scaffold thrombosis after CTO revascularization.

CASE REPORT

A 53-year-old male patient, with hypertension and dyslipidemia, presented with anterior ST-elevation myocardial infarction, 28 mo after elective percutaneous coronary intervention (PCI) of the chronically occluded left anterior descending artery (LAD), with implantation of 4 marker-to-marker bioresorbable vascular scaffolds (BVS, Absorb Abbott Vascular, Abbott Park, Illinois), performed in another cath-lab. BVS implantation followed chronic total occlusion (CTO) recanalization unintentionally performed according the subintimal tracking and re-entry (STAR) technique. The dissected segment was only partially sealed up to the distal segment of the LAD (Figure 1). The patient completed 18 mo of dual antiplatelet therapy (DAPT) 10 mo before his presentation at the emergency room. The

index coronary angiography showed a large thrombus at the proximal segment of the proximal BVS followed by a long dissection up to the very distal LAD segment (Figure 2). Thrombus aspiration and proximal drug eluting stent (DES) implantation was performed, while medical treatment was suggested for the distal chronic dissection (Figure 3). DAPT with ASA and Ticagrelor was finally resumed and clinical follow up planned.

DISCUSSION

To the best of our knowledge, this is the first clinical case reporting on a very late scaffold thrombosis and reoccurrence of coronary dissection after PCI of a chronic coronary total occlusion. Since neither optical coherence tomography (OCT) nor intravascular ultrasound (IVUS) were available at the time of both baseline and index procedures, the mechanism subtending the BVS failure in this particular case remains unknown. However, we might speculate that intraluminal scaffold dismantling together with scaffold discontinuity and restenosis during the resorption process, might have been responsible of thrombus formation at the mid-LAD, as previously described^[1-3]. In addition, the gradual scaffold resorption process, together with the incomplete scaffold coverage of the dissected segment at the time of the CTO PCI, might have been responsible of incomplete dissection healing, with progressive expansion of the subintimal hematoma, resulting in a "dual lumen" coronary artery^[4,5]. CTOs are the most challenging coronary lesions for PCI, mainly because of two reasons: (1) Procedure related: CTO remains technically challenging, in fact PCI failure is reported in up to 35% of CTOs and > 40% of CTOs are not attempted and treated either with medical therapy or with CABG; (2) Patient related: Identification of those patients for whom PCI of CTO does not bring any significant clinical benefit, despite successful revascularization, is still debatable^[6]. By the way, the use of BVS for CTO revascularization is particularly appealing mainly because PCI normally involves long coronary segments, thereby limiting future surgical interventions and increasing the risk of late malapposition after Drug Eluting Stents (DES) implantation^[7,8]. However, limited data are available about the use of BVS for PCI of CTOs. In fact, most of the randomized controlled trials conducted so far compared BVS and DES in simple or intermediate coronary artery stenosis, thereby the long-term efficacy of such new devices for percutaneous revascularization of complex stenosis, such as CTOs is still not clear. Recently, a propensity score adjusted analysis of 537 patients undergoing to PCI of a CTO showed a trend toward a higher adjusted risk of ischemia-driven target lesion revascularization for patients undergoing to BVS implantation as compared with DES^[9]. However, larger randomized studies are warrant in order to better define the role of BVS in CTO-PCI.

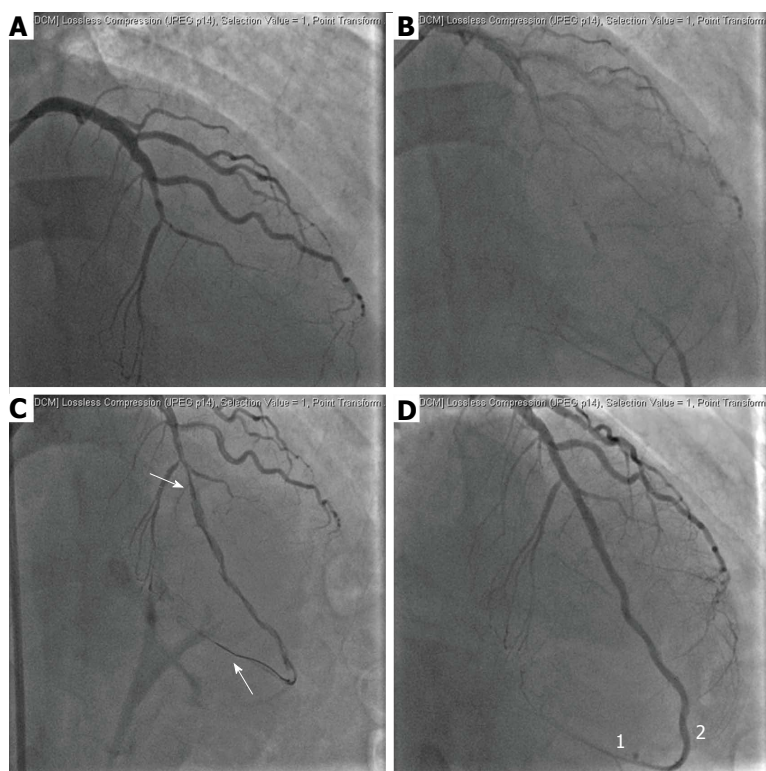


Figure 1 Baseline chronic total occlusion-percutaneous revascularization of the left anterior descending. A and B: Mid-LAD occlusion with omolateral reperfusion of the distal segment; C: Dissected segment after CTO recanalization and balloon dilation (white arrows); D: Final result after four BVS implantation and (2) contrast staining at the distal LAD suggesting the presence of subintimal hematoma with the occlusion of the distal apical branch (1). BVS: Bioresorbable vascular scaffolds; LAD: Left anterior descending; CTO: Chronic total occlusion.

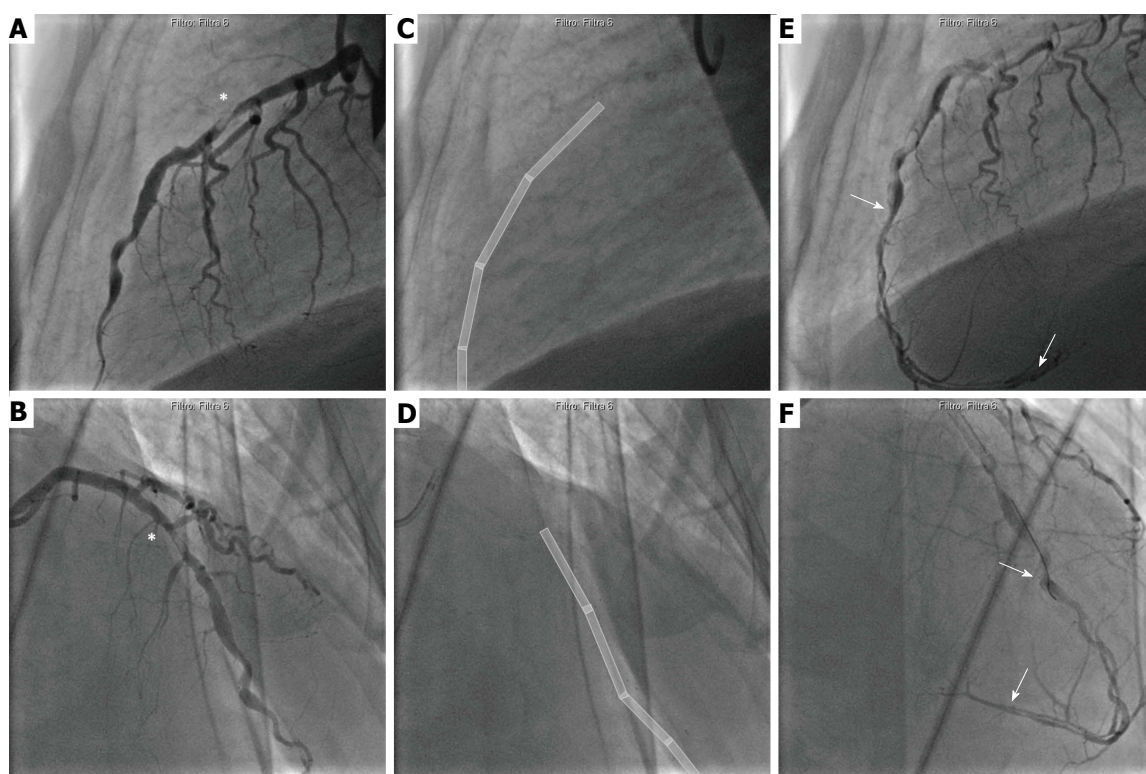


Figure 2 Coronary angiography of the left anterior descending at 28 mo after chronic total occlusion recanalization. A and B: Large in-scaffold thrombus at the proximal edge of the previously implanted BVS (C, D, white boxes), at the mid LAD (*); E and F: Dissected segment (white arrows) from the mid-LAD up to the distal segment, with a resulting image of a "dual lumen" LAD. LAD: Left anterior descending; BVS: Bioresorbable vascular scaffolds.

Conclusion

This case raises concerns about the risk of very late scaffold thrombosis and the use of BVS in complex CTO-PCI, particularly when "full polymer jacket" is not

warranted for the entire dissected coronary segment. A prolonged DAPT should be encouraged while a complete sealing of the dissected segment should be considered^[10].

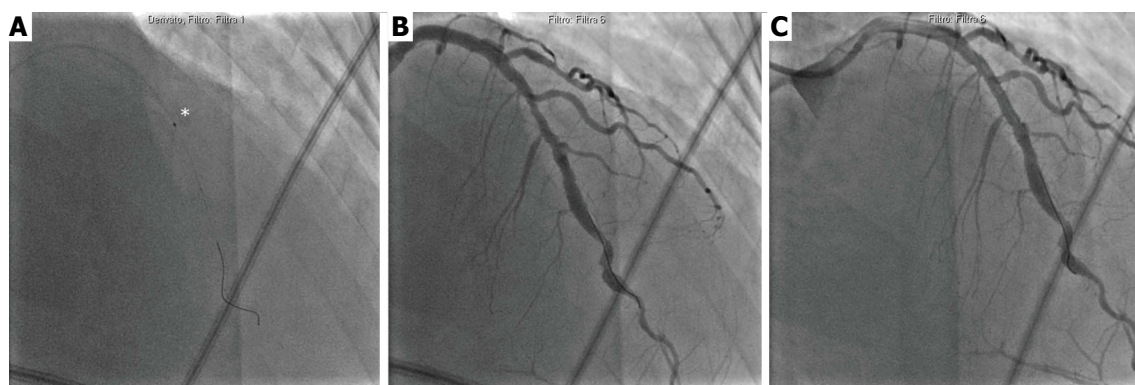


Figure 3 Percutaneous revascularization of the left anterior descending. A and B: After coronary wire crossing, thrombus aspiration was successfully performed (*) and a drug eluting stent was finally implanted with good final result (C).

COMMENTS

Case characteristics

A 53-year-old male patient presenting with chest pain for an anterior ST-elevation myocardial infarction.

Clinical diagnosis

Anterior ST-elevation myocardial infarction due to very late scaffold thrombosis.

Differential diagnosis

Clinical characteristic, patient's medical history and echocardiography were useful for differential diagnosis between pericarditis and aortic dissection.

Laboratory diagnosis

High sensitive Troponin-I increased together with myoglobin and creatine kinase-MB.

Imaging diagnosis

Definite diagnosis was possible with invasive coronary angiography which showed a large thrombus at the proximal segment of the proximal bioresorbable vascular scaffolds (BVS) followed by a long dissection up to the very distal left anterior descending segment.

Pathological diagnosis

In the acute setting of the coronary syndrome, no thrombus was kept for pathological analysis.

Treatment

Thrombus aspiration and proximal drug eluting stent implantation was performed, while medical treatment was suggested for the distal chronic dissection.

Related reports

To our knowledge, there are only few case reports about very late scaffold thrombosis.

Experiences and lessons

This case raises concerns about the use of BVS in complex chronic total occlusion percutaneous revascularization (PCI), thereby suggesting a prolonged dual-antiplatelet therapy tailored according to both patients' clinical characteristics and PCI procedures.

Peer-review

This case report of late thrombosis after chronic total occlusion recanalization with bioabsorbable scaffold is well organized.

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