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EDITORIAL

Thrombosis: Novel nanomedical concepts of diagnosis and treatment

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Abstract

Intravascular thrombosis, a critical pathophysiological feature of many cardiovascular disorders, leads to the formation of life-threatening obstructive blood clots within the vessels. Rapid recanalization of occluded vessels is essential for the patients' outcome, but the currently available systemic fibrinolytic therapy is associated with low efficacy and tremendous side effects. Additionally, many patients are ineligible for systemic thrombolytic therapy, either due to delayed admission to the hospital after symptom onset, or because of recent surgery, or bleeding. In order to improve the treatment efficacy and to limit the risk of hemorrhagic complications, both precise imaging of the affected vascular regions, and the localized application of fibrinolytic agents, are required. Recent years have brought about considerable advances in nanomedical approaches to thrombosis. Although these thrombus-targeting imaging agents and nanotherapies are not yet implemented in humans, substantial amount of successful *in vivo* applications have been reported, including animal models of stroke, acute arterial thrombosis, and pulmonary embolism. It is evident that the future progress in diagnosis and treatment of thrombosis will be closely bound with the development of novel nanotechnology-based strategies. This Editorial focuses on the recently reported approaches, which hold a great promise for personalized, disease-targeted treatment and reduced side effects in the patients suffering from this life-threatening condition.

Key words: Thrombosis; Thrombus imaging; Nanomedicine; Targeted nanoparticles; Thrombolytic drug-delivery systems

Core tip: The prevalence of thrombosis, the formation of life-threatening clots obstructing vital blood vessels, continues to rise. Accurate diagnosis and rapid recanalization of an occluded artery is essential to improve outcomes and reduce the mortality in acute myocardial infarction or stroke. The current thrombolytic therapy often fails to diminish the occlusion and is associated with a high rate of hemorrhagic complications. Develop-

ment of directed nanosystems for local thrombolysis, characterized by a strong fibrinolytic effect and low bleeding risk, is therefore one of the most urgent tasks in the prevention and the therapy of acute thrombotic events.

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INTRODUCTION

Intravascular thrombosis, the formation of life-threatening obstructive blood clots within the vessels, underlies a number of cardiovascular disorders such as heart attack, ischemic stroke, pulmonary embolism, and deep vein thrombosis[1,2]. Among these, atherothrombotic diseases (ischemic heart disease and stroke) are collectively responsible for 25% of all deaths worldwide[3]. In contrast, the burden of venous thromboembolism (VTE) is not well documented. According to the recent analyses[4], its incidence ranges between 1-2 per 1000 individuals in most of the studies, resembling the frequency of myocardial infarction[5], and the deaths due to VTE are estimated at 300000 per year in the United States[6]. Globally, the prevalence of thrombotic disorders continues to increase, particularly in the developing countries. However, despite significant advances in understanding of the disease mechanisms, which led to the development of more effective anti-thrombotic and thrombolytic drugs[7], the effect of these therapies on the patients' outcomes remains disappointing: According to the published data, less than 25% of high cardiovascular risk patients receiving antiplatelet therapy avoided a fatal thrombotic event[8]. The inherent problem with the conventional antithrombotic approaches is the increased risk of bleeding, as the existing therapeutics destabilize hemostatic processes. Among the most urgent challenges in this field are thus (1) identification of patients at increased risk for thrombosis and precise estimation of individual disease burden, as well as (2) development of safe and effective strategies to prevent thrombotic events and/or rapidly diminish vascular occlusion. These challenges have been intensively addressed by the researchers across the globe, resulting in a number of innovative approaches to diagnosis and treatment of thrombosis, as outlined below.

DIAGNOSIS OF THROMBOTIC DISEASE

Individual burden of thrombosis

In order to improve the diagnosis, risk stratification, and management of thrombotic syndromes, reliable methods of *in vivo* assessment of the thrombotic risk in patients with cardiovascular diseases are needed. Although thrombin is the most important serine protease within the coagulation cascade[9], thus far the diagnostic tests are lacking that are able to rapidly and reliably assess its activity in clinical settings. To address this need, a novel urinary nanomarker assay based on thrombin-sensitive iron oxide nanoparticles was recently developed that allows detection of thrombin activity and thus quantitative estimation of thrombosis burden *in vivo*[10]. The nanomarkers were produced by coupling iron oxide nanoworms with thrombin-cleavable peptides linked to a synthetic reporter system, composed of the protease-resistant peptide, glutamate-fibrinopeptide B, which was modified at the termini with ligands detectable by an immunoassay (fluorescein, or Alexa488, and biotin). In a mouse model of pulmonary embolism induced by thromboplastin[11], the circulating nanomarkers sucessfully accessed the local sites of thrombosis and released the reporters upon cleavage by thrombin. The urinary clearance of these reporters was detectable by ELISA with high sensitivity and significantly correlated with the thrombosis burden estimated by the histochemically analyzed amount of fibrin deposited in the lungs[10]. Given the need of rapid and reliable *in vivo* assessment of the thrombotic burden in cardiovascular patients, this urine analysis-based assay represents a very promising platform for use in clinical practice.

Imaging of thrombosis in vivo

During the thrombotic event, initially smaller clots form larger obstructive thrombi, which require a long time for recanalization, and a high dose of thrombolytic agents, or a high rate of mechanical clot disruption[12]. Both the burden and the localization[13,14] of thrombi are known to affect clinical outcomes and mortality[12,15]. By providing essential information about the size and localization of the thrombi, direct thrombus imaging would have an immense impact on clinical practice: Without a tool for *in vivo* imaging in the clinical settings, individualisation of the thrombolytic therapy is impossible. The recommended fixed dose of intravenous tissue plasminogen activator (tPA; 0.9 mg/kg) is thus insufficient in some patients, resulting in resistance to thrombolysis, or excessive in others, leading to increased risk of hemorrhagic complications.

Intravascular thrombus formation therefore represents a target for novel nanoparticle-based diagnostics. As early as in 2001, thrombus detection *in vivo* by magnetic resonance imaging (MRI) was accomplished in dogs using anti-fibrin monoclonal antibodies conjugated to lipid-encapsulated perfluorocarbon nanoparticles containing gadolinium-chelate[16]. More recently, *ex vivo* optical imaging of atherothrombosis in ApoE-deficient mice fed a high-fat diet was reported with lipopeptide nanoparticles carrying a fluorescently-labeled pentapeptide Cys-Arg-Glu-Lys-Ala (CREKA), which binds to clotted plasma proteins in the blood vessels[17]. Intravascular fibrin detection by MRI in this mouse model was also described by Makowski *et al*[18]

using a commercially available gadolinium-based fibrin-binding peptide EP-2104R. Another fibrin-targeting peptide (GPR, Gly-Pro-Arg) has been utilised in studies by Obermeyer *et al*[19] and McCarthy *et al*[20]. The former group applied bacteriophage MS2 capsids functionalized with GPR peptide on the exterior of each protein shell for fibrin imaging. The GPR-modified capsids were evaluated *in vitro* with regard to the fibrin imaging. Near-infrared fluorophores on the interior surface of the capsids enabled optical detection of their binding to fibrin clots with improved signal-to-background ratio as compared with non-targeted nanoagents[19]. Furthermore, in a mouse model of ferric chloride injury to jugular vein, McCarthy *et al*[20] utilised fluorescently labeled cross-linked iron oxide nanoparticles functionalized with GPR or FXIIIa-targeting peptides to obtain multimodal nanoagents exhibiting either covalent or noncovalent binding to thrombi. These nanosystems allowed *in vivo* detection of thrombus by both MRI and optical imaging modalities.

Apart from fibrin, activated platelets represent an important target for detection of intraluminal thrombi and endothelial activation, a marker of ongoing atherothrombotic disease. Therefore, the development of contrast agents for imaging of P-selectin, expressed by activated platelets, has been the aim of numerous efforts. In particular, the research group of Bachelet *et al*[21] and Manzo-Silberman *et al*[22] developed several nanosystems for *in vivo* P-selectin detection based on polysaccharide fucoidan (a mimic of sialyl Lewis X, the natural ligand of P-selectin) derived from brown seaweed. Radiolabeled fucoidan was demonstrated a suitable P-selectin targeting agent for *in vivo* single-photon emission computed tomography imaging of platelet-rich thrombi in rat models of infective endocarditis and elastase-induced aortic aneurysms, as well as endothelial activation in a model of myocardial ischemia-reperfusion[23]. Very recently, this group tested ultrasmall superparamagnetic iron oxide nanoparticles (USPIO) coated with fucoidan for molecular MRI of intraluminal thrombus: In a rat model of elastase-induced aortic aneurysms, all thrombi detected in MRI by USPIO-fucoidan particles were correlated with P-selectin immunostaining and USPIO detection by electron microscopy, whereas no intraluminal thrombi were detectable upon control USPIO[24]. In a study by Ta *et al*[25], iron oxide nanoparticles were coupled with a single-chain antibody that specifically binds to ligand-induced binding sites (LIBS) on glycoprotein IIb/IIIa (CD41/CD61), the most highly expressed molecules on the surface of activated platelets. LIBS-targeting nanocontructs showed a strong and specific binding to activated platelets *in vitro*, as well as *in vivo* by intravital microscopy and MRI of mouse carotid arteries[25].

Iron oxide nanoparticles allow *in vivo* visualization of thrombi with MRI. However, MRI is rarely the test of choice for the management of patients with acute thrombotic events, due to the time restrictions of clinical management, or contraindications for MRI in some patients. For most clinical decision making involving the administration of tPA, computed tomography (CT) is the current standard[26] due to its speed and convenience. However, non-contrast CT often does not allow a precise assessment of extent and distribution of thromboemboli, because the density of the thrombus is often not much different from that of the surrounding blood. Therefore, efficient and safe contrast agents are needed to achieve the enhancement of thrombus imaging with the clinical CT. Addressing this issue, thrombus detection using microCT has been recently tested in a mouse model of ferric chloride-induced carotid thrombosis utilising glycol chitosan (GC)-gold nanoparticles as contrast agents[27]. The study showed that these nanoparticles became trapped in the blood clots proportionally to thrombotic insult, and allowed the quantitative characterization and serial monitoring of thrombus evolution, embolization, and *in situ* recurrent thrombosis, as well as the assessment of therapeutic efficacy of tPA-induced thrombolysis. Due to a long circulating half-life, GC-gold nanoparticles remained available for entrapment into fibrin matrix for up to 3 wk, allowing repetition or ongoing monitoring of thrombogenesis and thrombolysis with microCT[27].

Collectively, the above-discussed studies demonstrate that nanosystems which target fibrin or activated platelets can enhance the detection and the diagnosis of intravascular thrombi by means of existing imaging modalities. Thus far however, little is known about their safety and efficacy in humans. Provided low toxicity and a good therapeutic index, these nanosystems should improve risk stratification when translated into the clinical practice, and allow personalized therapeutic regimen in thrombosis-related diseases.

PREVENTION AND TREATMENT OF THROMBOSIS

Current therapies

Platelet activation and aggregation are the key processes involved in thrombosis and thromboembolic disorders. The best preventive measures for the thrombotic events in the risk patients are thus antiplatelet or anticoagulation therapy. Although aspirin still plays an essential role in the primary and secondary prevention of atherothrombosis, new generation antithrombotic therapies are rapidly evolving. In combination with aspirin, ADP $P2Y_{12}$ receptor antagonists are used in the management of acute coronary syndromes and percutaneous coronary interventions in order to prevent adverse cardiac events and stent thrombosis[28]. Oral anticoagulation used for the treatment of VTE and for the prevention of emboli in patients with atrial fibrillation has advanced with the use of direct thrombin and factor Xa inhibitors that do not require therapeutic monitoring[29]. Although antiplatelet and anticoagulant therapy is essential for the primary and secondary prevention of atherothrombosis, systemic pre-treatment

with antithrombotic agents is associated with increased risk of hemorrhagic complications after intravenous thrombolysis in patients with acute ischemic stroke[30].

Acute management of stroke focuses on stabilizing the patient and ensuring the maximal reperfusion of the ischemic brain tissue. Hence, intravenous thrombolysis remains the mainstay treatment for acute ischemic stroke: A statistically and clinically significant improvement in outcomes is observed for carefully selected patients treated with tPA within 4.5 h of stroke onset[31]. While no other medication has demonstrated comparable efficacy, tPA remains the only drug for acute ischemic stroke approved by Food and Drug Administration since 1996[32]. However, its use is very limited both by the narrow eligibility and administration window, and by the risk of hemorrhagic complications[33], so called thrombolysis-related symptomatic intracerebral haemorrhage, which occurs in about 6% of patients and is associated with nearly 50% mortality[34,35]. Additionally, in some patients eligible for tPA treatment, the outcome is poor, when occlusion occurs in large arteries (internal carotid artery, middle cerebral artery or basilar artery). For these subgroups of stroke patients, an endovascular (intraarterial) administration route has been developed, but its clinical benefit remains unproven. Randomized controlled clinical trials did not show any added benefit of endovascular treatment over intravenous tPA alone in intravenous tPA-eligible patients, even in patients with persistent large-artery occlusion, nor have these trials provided evidence of clinical benefit in patients who were ineligible for intravenous tPA because of being > 4.5 h from symptom onset[36].

Alternative means of reperfusion, ideally based on individual thrombus burden estimation are therefore needed. For this purpose, thrombus-targeted nanosystems could serve as carriers for direct delivery of therapeutic agents to the occlusive thrombi in order to increase the effective local concentrations of antithrombotic drugs.

Antiplatelet and anticoagulant medications for prevention of thrombosis

Current antiplatelet drugs are only partially effective in preventing thrombus formation and thromboembolic events. Consequently, much interest is drawn both to the discovery of novel antiplatelet medications and to the optimization of the existing ones. The group of Chen *et al*[37] reported the synthesis of novel, self-assembly anti-platelet aggregation peptides containing L-arginine and L-aspartic acid, that were complexed with Cu(Ⅱ) to form stable nanoparticles. In a rat model of thrombus formation, these peptides at 5 μmol/kg achieved anti-thrombotic activity comparable to 110 μmol/kg aspirin, whereas the peptide-Cu(Ⅱ)-nanocomplexes were equally effective in reducing the thrombus weight already at 100-fold lower concentrations (0.05 μmol/kg). More recently, the same group reported a successful approach to overcome the low response to aspirin observed in some patients, which severely decreases its efficacy at the tolerated doses[38]. In that study, aspirin was conjugated to the Arg-Gly-Asp-Val (RGDV) tetrapeptide, resulting in a nano-assembly targeting glycoprotein Ⅱb/Ⅲa, the receptor for RGD peptide on the surface of the activated platelets. *In vitro*, aspirin-RGDV particles inhibited platelet aggregation induced by thrombin or arachidonic acid more effectively than free aspirin. A very strong antithrombotic effect of aspirin-RGDV was also observed in a rat model of thrombosis - whereas aspirin exhibited no antithrombotic activity at 16.7 μmol/kg, aspirin-RGDV significantly and dose-dependently inhibited thrombus formation in the treated rats already at doses of 0.1 and 1 nmol/kg[38]. Targeted delivery of aspirin to thrombus and its local release to activated platelets thus resulted in an extraordinarily potent inhibition of thrombus formation, overcoming the apparent non-response to aspirin. Formation of thrombi was also effectively prevented by novel heparin-conjugated carbon nanocapsules in a mouse model of acute hindlimb thromboembolism[39]. Compared to the injection of heparin alone, those heparin-functionalized carbon nanocapsules displayed superior antithrombotic activity *in vitro* and *in vivo*, representing a promising nanocarrier system for anticoagulant delivery.

Some of the most common cardiovascular interventions, including stent implantation or prosthetic heart valve replacement, are associated with increased risk of thrombosis, necessitating prolonged or even lifelong antiplatelet therapy. Particularly after cessation or premature discontinuation of the therapy, the incidence of thrombosis is high. Gene therapy is considered a safe strategy to increase the local expression of thrombolytic agents over an extended period of time, in parallel reducing the systemic risk of hemorrhagic complications. Ji *et al*[40] used a chitosan nano-*tPA* gene plasmid to locally transfect dog cardiomyocytes at the time of mechanical heart valve replacement. The transfected gene significantly increased the survival of animals and prevented thrombus formation on mechanical valves, without affecting systemic hemostasis. In a further study by the same group[41], the *tPA* gene plasmid was packaged in albumin nanoparticles crosslinked to ultrasonic microbubbles. Following intravenous administration, a local therapeutic ultrasound treatment of the heart after valve replacement had been performed, which resulted in increased myocardial expression of *tPA* and prevented thrombosis for 8 wk after operation.

Thrombolytic therapies

Rapid recanalization of thrombus-occluded arteries is essential to improve outcomes and reduce the mortality in acute myocardial infarction or stroke. Development of delivery systems for local thrombolysis is therefore one of the most urgent tasks in the prevention and the therapy of acute thrombotic events. Within the coagulation cascade, thrombin represents the most important target of direct anticoagulants. As an

example, hirulog, an analogue of the natural thrombin inhibitor hirudin was locally delivered to the thrombus using lipid nanoparticles containing a fibrin-binding peptide. Upon administration of the fibrin-targeting hirulog-carrying particles, significantly higher levels of antithrombin activity were achieved in the aortic tree of ApoE-deficient mice as compared with non-targeted particles[17].

The effects of another potent thrombin inhibitor, d-phenylalanyl-l-prolyl-l-arginyl-chloromethyl ketone (PPACK) were investigated the group of Myerson *et al*[42] and Palekar *et al*[43] in a mouse model of acute arterial thrombosis due to photochemical injury of the carotid artery. Perfluorocarbon nanoparticle-bound PPACK outperformed both heparin and uncomplexed PPACK in inhibiting thrombosis, and formed a local clotting barrier that remained effective even as systemic effects rapidly diminished[42]. Similarly, PPACK-liposomes administered prior to the arterial injury significantly delayed the time to arterial occlusion as compared to free PPACK. Whereas systemic anticoagulant profiles returned to control levels within 50 min, the inhibition of thrombus formation was maintained at the injury site beyond 2 h[43]. The establishment of a potent and long-acting anticoagulant surface over a newly forming clot with the use of thrombin targeted nanoparticles offers an alternative site-targeted approach to the management of acute thrombosis.

As described in detail above, intravenous infusion of tPA is characterized by several drawbacks, including low efficacy combined with a high risk of bleeding complications[35]. Therefore, several innovative strategies aiming at targeted and/or local applications of plasminogen activators have been designed. The possibility of magnetic-targeting of tPA for local thrombolysis was investigated by Ma *et al*[44] in a rat embolic model. Magnetite nanoparticles bound to tPA (tPA equivalent of 0.2 mg/kg) were administered intraarterially under guidance of an external magnet moving along the iliac artery. Magnetic tPA-nanoparticles accumulated in the thrombus-affected region and achieved an effective target thrombolysis with < 20% of a regular dose of free tPA. Another tPA delivery nanosystem comprising basic gelatin and zinc acetate was tested by Kawata *et al*[45] in a swine acute myocardial infarction model. Within this nanosystem, tPA activity was reduced *in vitro* to approximately 50% of free tPA and was fully recoverable by transthoracic ultrasound application. In comparison to treatment with free tPA (0.447 mg/kg), which recanalized the occluded coronary artery in only 1 of 10 swine, nanoparticles containing the same dose of tPA with ultrasound activation achieved recanalization in 9 of 10 swine within 30 min, suggesting that this nanosystem bears promising potential for improved intravenous thrombolysis.

In attempt to create a theranostic construct with fibrinolytic activity, McCarthy *et al*[46] synthesized a multimodal nanoagent using magnetofluorescent crosslinked dextran-coated iron oxide nanoparticles conjugated to tPA. Thrombus-targeting was achieved by nanoparticle functionalization with an activated FXIIIa-sensitive peptide. In murine models of arterial and venous thrombosis, the FXIIIa-targeted fibrinolytic nanoagent efficiently bound the margin of intravascular thrombi as detected by intravital fluorescence microscopy. The fibrinolytic activity of the nanoagent compared to free tPA was subsequently evaluated in a murine model of pulmonary embolism, showing that the FXIIIa-targeted agent lysed pulmonary emboli with similar efficacy as free tPA[46].

Targeted tPA delivery to stenotic arteries by employing universal hemodynamic phenomena was described by Korin *et al*[47]. Since occlusions in blood vessels result in local increases in shear stress, the authors designed micro-aggregates of poly-lactic-glycolic acid nanoparticles coated with tPA. Under physiologic flow conditions with shear stress values up to 70 dyn/cm^2, these micro-aggregates remained stable, but the exposure to abnormally high shear stress in the regions of vascular occlusion/stenosis resulted in their rapid break up followed by local drug release. As compared with free drug, the shear-activated tPA-coated nanoparticles rapidly dissolved the ferric chloride-induced arterial thrombi in mouse mesenteric arteries, with complete clearance of occluding thrombi within 5 min after application[47]. Moreover, upon infusion of lethally large fibrin clots, the immediate application of the shear-activated tPA-coated nanoparticles increased survival by 80%. The doses of shear-activated tPA-nanoparticles required for clot dissolution were about 100-times lower than the doses required for achieving comparable effects with free drug[47]. This strategy, utilizing a universal hemodynamic phenomenon of increased shear stress upon reduction in vessel diameter should result in a broad applicability for all occlusive vascular conditions, including *e.g.,* treatment of stenotic atherosclerotic plaques, pulmonary emboli, and ischemic stroke.

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, remains a common and potentially life-threatening disease[48]. Standard treatments aim to minimize acute morbidity and mortality by preventing the potentially fatal embolization of the initial thrombus and to reduce the long-term complications of post-thrombotic syndrome. For patients with VTE, catheter-based revascularization therapy [catheter-directed thrombolysis (CDT)] has emerged as favoured means of administration replacing systemic thrombolysis. Urokinase-type plasminogen activator (uPA) is commonly used for CDT in the clinical settings of VTE. However, similar to arterial thrombosis treatment, strict eligibility criteria are necessary to reduce the risk of bleeding complications, which limit the applicability of this therapy. To minimize the adverse effects and increase therapeutic benefits, Jin *et al*[49] produced uPA-coated, self-assembled chitosan and tripolyphosphate nanoparticles. In a

rabbit model of thrombosis, a significant improvement in the thrombolytic effect compared with free uPA was observed upon administration of uPA-carrying nanoparticles. Additionally, the study confirmed the superiority of CDT for improving clot lysis and minimizing adverse effects over drug-induced systemic thrombolysis.

CONCLUSION

The potential clinical impact of nanotechnology in terms of thrombosis prevention and management is enormous. But in spite of the promising results obtained in the vast number of bench investigations that have been published in the recent years, the thrombus-targeting imaging nanoagents and fibrinolytic nanotherapies are not yet implemented in humans. To ensure clinical safety and feasibility, the intravascular diagnostic and drug-delivery systems must be subject to a close toxicologic and pharmacologic scrutiny prior to their application in patients. Thus, substantial amount of *in vivo* studies will be necessary before the successful basic research can be translated into clinical trials. Despite multiple safety and regulatory constraints, the future progress in diagnosis and treatment of thrombosis is expected to benefit strongly from the development of novel nanotechnology-based strategies.

REFERENCES

1 **Jackson SP**. Arterial thrombosis--insidious, unpredictable and deadly. *Nat Med* 2011; **17**: 1423-1436 [PMID: 22064432 DOI: 10.1038/nm.2515]

2 **Dimarsico L**, Cymet T. Pulmonary embolism--a state of the clot review. *Compr Ther* 2007; **33**: 184-191 [PMID: 18025610 DOI: 10.1007/s12019-007-8015-6]

3 **Lozano R**, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095-2128 [PMID: 23245604 DOI: 10.1016/S0140-6736(12)61728-0]

4 **Raskob GE**, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, Hylek EM, Kakkar A, Konstantinides SV, McCumber M, Ozaki Y, Wendelboe A, Weitz JI. Thrombosis: a major contributor to global disease burden. *Arterioscler Thromb Vasc Biol* 2014; **34**: 2363-2371 [PMID: 25304324 DOI: 10.1161/ATVBAHA.114.304488]

5 **Oger E**. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d' Etude de la Thrombose de Bretagne Occidentale. *Thromb Haemost* 2000; **83**: 657-660 [PMID: 10823257]

6 **Heit JA**. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol* 2008; **28**: 370-372 [PMID: 18296591 DOI: 10.1161/ATVBAHA.108.162545]

7 **McFadyen JD**, Jackson SP. Differentiating haemostasis from thrombosis for therapeutic benefit. *Thromb Haemost* 2013; **110**: 859-867 [PMID: 23945664 DOI: 10.1160/TH13-05-0379]

8 **Antithrombotic Trialists' Collaboration.** Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71-86 [PMID: 11786451]

9 **Davie EW**, Kulman JD. An overview of the structure and function of thrombin. *Semin Thromb Hemost* 2006; **32** Suppl 1: 3-15 [PMID: 16673262 DOI: 10.1055/s-2006-939550]

10 **Lin KY**, Kwong GA, Warren AD, Wood DK, Bhatia SN. Nanoparticles that sense thrombin activity as synthetic urinary biomarkers of thrombosis. *ACS Nano* 2013; **7**: 9001-9009 [PMID: 24015809 DOI: 10.1021/nn403550c]

11 **Lenain N**, Freund M, Léon C, Cazenave JP, Gachet C. Inhibition of localized thrombosis in P2Y1-deficient mice and rodents treated with MRS2179, a P2Y1 receptor antagonist. *J Thromb Haemost* 2003; **1**: 1144-1149 [PMID: 12871312]

12 **Barreto AD**, Albright KC, Hallevi H, Grotta JC, Noser EA, Khaja AM, Shaltoni HM, Gonzales NR, Illoh K, Martin-Schild S, Campbell MS, Weir RU, Savitz SI. Thrombus burden is associated with clinical outcome after intra-arterial therapy for acute ischemic stroke. *Stroke* 2008; **39**: 3231-3235 [PMID: 18772444 DOI: 10.1161/STROKEAHA.108.521054]

13 **Saqqur M**, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, Akhtar N, Orouk FO, Salam A, Shuaib A, Alexandrov AV. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke* 2007; **38**: 948-954 [PMID: 17290031 DOI: 10.1161/01.STR.0000257304.21967.ba]

14 **Sillanpää N**, Saarinen JT, Rusanen H, Elovaara I, Dastidar P, Soimakallio S. Location of the clot and outcome of perfusion defects in acute anterior circulation stroke treated with intravenous thrombolysis. *AJNR Am J Neuroradiol* 2013; **34**: 100-106 [PMID: 22723067 DOI: 10.3174/ajnr.A3149]

15 **Sillanpaa N**, Saarinen JT, Rusanen H, Hakomaki J, Lahteela A, Numminen H, Elovaara I, Dastidar P, Soimakallio S. The clot burden score, the Boston Acute Stroke Imaging Scale, the cerebral blood volume ASPECTS, and two novel imaging parameters in the prediction of clinical outcome of ischemic stroke patients receiving intravenous thrombolytic therapy. *Neuroradiology* 2012; **54**: 663-672 [PMID: 21904832 DOI: 10.1007/s00234-011-0954-z]

16 **Flacke S**, Fischer S, Scott MJ, Fuhrhop RJ, Allen JS, McLean M, Winter P, Sicard GA, Gaffney PJ, Wickline SA, Lanza GM. Novel MRI contrast agent for molecular imaging of fibrin: implications for detecting vulnerable plaques. *Circulation* 2001; **104**: 1280-1285

[PMID: 11551880 DOI: 10.1161/hc3601.094303]
17 **Peters D**, Kastantin M, Kotamraju VR, Karmali PP, Gujraty K, Tirrell M, Ruoslahti E. Targeting atherosclerosis by using modular, multifunctional micelles. *Proc Natl Acad Sci USA* 2009; **106**: 9815-9819 [PMID: 19487682 DOI: 10.1073/pnas.0903369106]
18 **Makowski MR**, Forbes SC, Blume U, Warley A, Jansen CH, Schuster A, Wiethoff AJ, Botnar RM. In vivo assessment of intraplaque and endothelial fibrin in ApoE(-/-) mice by molecular MRI. *Atherosclerosis* 2012; **222**: 43-49 [PMID: 22284956 DOI: 10.1016/j.atherosclerosis.2012.01.008]
19 **Obermeyer AC**, Capehart SL, Jarman JB, Francis MB. Multivalent viral capsids with internal cargo for fibrin imaging. *PLoS One* 2014; **9**: e100678 [PMID: 24960118 DOI: 10.1371/journal.pone.0100678]
20 **McCarthy JR**, Patel P, Botnaru I, Haghayeghi P, Weissleder R, Jaffer FA. Multimodal nanoagents for the detection of intravascular thrombi. *Bioconjug Chem* 2009; **20**: 1251-1255 [PMID: 19456115 DOI: 10.1021/bc9001163]
21 **Bachelet L**, Bertholon I, Lavigne D, Vassy R, Jandrot-Perrus M, Chaubet F, Letourneur D. Affinity of low molecular weight fucoidan for P-selectin triggers its binding to activated human platelets. *Biochim Biophys Acta* 2009; **1790**: 141-146 [PMID: 19026722 DOI: 10.1016/j.bbagen.2008.10.008]
22 **Manzo-Silberman S**, Louedec L, Meilhac O, Letourneur D, Michel JB, Elmadbouh I. Therapeutic potential of fucoidan in myocardial ischemia. *J Cardiovasc Pharmacol* 2011; **58**: 626-632 [PMID: 22146406 DOI: 10.1097/FJC.0b013e3182308c64]
23 **Rouzet F**, Bachelet-Violette L, Alsac JM, Suzuki M, Meulemans A, Louedec L, Petiet A, Jandrot-Perrus M, Chaubet F, Michel JB, Le Guludec D, Letourneur D. Radiolabeled fucoidan as a p-selectin targeting agent for in vivo imaging of platelet-rich thrombus and endothelial activation. *J Nucl Med* 2011; **52**: 1433-1440 [PMID: 21849401 DOI: 10.2967/jnumed.110.085852]
24 **Suzuki M**, Bachelet-Violette L, Rouzet F, Beilvert A, Autret G, Maire M, Menager C, Louedec L, Choqueux C, Sabourat P, Haddad O, Chauvierre C, Chaubet F, Michel JB, Serfaty JM, Letourneur D. Ultrasmall superparamagnetic iron oxide nanoparticles coated with fucoidan for molecular MRI of intraluminal thrombus. *Nanomedicine* (Lond) 2015; **10**: 73-87 [PMID: 24960075 DOI: 10.2217/nnm.14.51]
25 **Ta HT**, Prabhu S, Leitner E, Jia F, von Elverfeldt D, Jackson KE, Heidt T, Nair AK, Pearce H, von Zur Muhlen C, Wang X, Peter K, Hagemeyer CE. Enzymatic single-chain antibody tagging: a universal approach to targeted molecular imaging and cell homing in cardiovascular disease. *Circ Res* 2011; **109**: 365-373 [PMID: 21700932 DOI: 10.1161/CIRCRESAHA.111.249375]
26 **Latchaw RE**, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, Higashida RT, Hobson R, Kidwell CS, Koroshetz WJ, Mathews V, Villablanca P, Warach S, Walters B. Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. *Stroke* 2009; **40**: 3646-3678 [PMID: 19797189 DOI: 10.1161/STROKEAHA.108.192616]
27 **Kim DE**, Kim JY, Sun IC, Schellingerhout D, Lee SK, Ahn CH, Kwon IC, Kim K. Hyperacute direct thrombus imaging using computed tomography and gold nanoparticles. *Ann Neurol* 2013; **73**: 617-625 [PMID: 23495101 DOI: 10.1002/ana.23849]
28 **Depta JP**, Bhatt DL. New approaches to inhibiting platelets and coagulation. *Annu Rev Pharmacol Toxicol* 2015; **55**: 373-397 [PMID: 25562644 DOI: 10.1146/annurev-pharmtox-010814-124438]
29 **Ageno W**, Spyropoulos AC, Turpie AG. Role of new anticoagulants for the prevention of venous thromboembolism after major orthopaedic surgery and in hospitalised acutely ill medical patients. *Thromb Haemost* 2012; **107**: 1027-1034 [PMID: 22437976 DOI: 10.1160/TH11-11-0787]
30 **Dorado L**, Millán M, de la Ossa NP, Guerrero C, Gomis M, López-Cancio E, Ricciardi AC, Dávalos A. Influence of antiplatelet pre-treatment on the risk of intracranial haemorrhage in acute ischaemic stroke after intravenous thrombolysis. *Eur J Neurol* 2010; **17**: 301-306 [PMID: 19912320 DOI: 10.1111/j.1468-1331.2009.02843.x]
31 Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; **333**: 1581-1587 [PMID: 7477192 DOI: 10.1056/NEJM199512143332401]
32 **Chapman SN**, Mehndiratta P, Johansen MC, McMurry TL, Johnston KC, Southerland AM. Current perspectives on the use of intravenous recombinant tissue plasminogen activator (tPA) for treatment of acute ischemic stroke. *Vasc Health Risk Manag* 2014; **10**: 75-87 [PMID: 24591838 DOI: 10.2147/VHRM.S39213]
33 **Zhang J**, Yang Y, Sun H, Xing Y. Hemorrhagic transformation after cerebral infarction: current concepts and challenges. *Ann Transl Med* 2014; **2**: 81 [PMID: 25333056 DOI: 10.3978/j.issn.2305-5839.2014.08.08]
34 **Yaghi S**, Eisenberger A, Willey JZ. Symptomatic intracerebral hemorrhage in acute ischemic stroke after thrombolysis with intravenous recombinant tissue plasminogen activator: a review of natural history and treatment. *JAMA Neurol* 2014; **71**: 1181-1185 [PMID: 25069522 DOI: 10.1001/jamaneurol.2014.1210]
35 **Miller DJ**, Simpson JR, Silver B. Safety of thrombolysis in acute ischemic stroke: a review of complications, risk factors, and newer technologies. *Neurohospitalist* 2011; **1**: 138-147 [PMID: 23983849 DOI: 10.1177/1941875211408731]
36 **Powers WJ**. Endovascular (intraarterial) treatment of acute ischemic stroke: efficacy not supported by clinical trials. *South Med J* 2014; **107**: 101-106 [PMID: 24926676 DOI: 10.1097/SMJ.0000000000000054]
37 **Chen Y**, Cui G, Zhao M, Wang C, Qian K, Morris-Natschke S, Lee KH, Peng S. Synthesis, nano-scale assembly, and in vivo anti-thrombotic activity of novel short peptides containing L-Arg and L-Asp or L-Glu. *Bioorg Med Chem* 2008; **16**: 5914-5925 [PMID: 18495483 DOI: 10.1016/j.bmc.2008.04.064]
38 **Jin S**, Wang Y, Zhu H, Wang Y, Zhao S, Zhao M, Liu J, Wu J, Gao W, Peng S. Nanosized aspirin-Arg-Gly-Asp-Val: delivery of aspirin to thrombus by the target carrier Arg-Gly-Asp-Val tetrapeptide. *ACS Nano* 2013; **7**: 7664-7673 [PMID: 23931063 DOI: 10.1021/nn402171v]
39 **Tang AC**, Chang MY, Tang ZC, Li HJ, Hwang GL, Hsieh PC. Treatment of acute thromboembolism in mice using heparin-conjugated carbon nanocapsules. *ACS Nano* 2012; **6**: 6099-6107 [PMID: 22713482 DOI: 10.1021/nn301198r]
40 **Ji S**, Jun J, Xiaohan Y, Xia H, Xiaolei W, Xiaoqing Y, Jianzhou G, Wenping L, Yanhui Z. Study on construction of nano tPA plasmid to prevent thrombosis after mechanical valve replacement in dogs. *J Surg Res* 2011; **168**: e1-e5 [PMID: 20605599 DOI: 10.1016/j.jss.2010.01.011]
41 **Ji J**, Ji SY, Yang JA, He X, Yang XH, Ling WP, Chen XL. Ultrasound-targeted transfection of tissue-type plasminogen activator gene carried by albumin nanoparticles to dog myocardium to prevent thrombosis after heart mechanical valve replacement. *Int J Nanomedicine* 2012; **7**: 2911-2919 [PMID: 22787391 DOI: 10.2147/IJN.S32363]
42 **Myerson J**, He L, Lanza G, Tollefsen D, Wickline S. Thrombin-inhibiting perfluorocarbon nanoparticles provide a novel strategy for the treatment and magnetic resonance imaging of acute thrombosis. *J Thromb Haemost* 2011; **9**: 1292-1300 [PMID: 21605330 DOI: 10.1111/j.1538-7836.2011.04339.x]
43 **Palekar RU**, Myerson JW, Schlesinger PH, Sadler JE, Pan H, Wickline SA. Thrombin-targeted liposomes establish a sustained localized anticlotting barrier against acute thrombosis. *Mol Pharm* 2013; **10**: 4168-4175 [PMID: 24063304 DOI: 10.1021/mp400210q]
44 **Ma YH**, Wu SY, Wu T, Chang YJ, Hua MY, Chen JP. Magnetically targeted thrombolysis with recombinant tissue plasminogen activator bound to polyacrylic acid-coated nanoparticles. *Biomaterials* 2009; **30**: 3343-3351 [PMID: 19299010 DOI: 10.1016/j.biomaterials.2009.02.034]
45 **Kawata H**, Uesugi Y, Soeda T, Takemoto Y, Sung JH, Umaki K, Kato K, Ogiwara K, Nogami K, Ishigami K, Horii M, Uemura S, Shima M, Tabata Y, Saito Y. A new drug delivery system for intravenous coronary thrombolysis with thrombus targeting and stealth activity recoverable by ultrasound. *J Am Coll Cardiol* 2012; **60**: 2550-2557 [PMID: 23158532 DOI: 10.1016/j.jacc.2012.08.1008]
46 **McCarthy JR**, Sazonova IY, Erdem SS, Hara T, Thompson BD, Patel P, Botnaru I, Lin CP, Reed GL, Weissleder R, Jaffer FA. Multifunctional nanoagent for thrombus-targeted fibrinolytic

therapy. *Nanomedicine* (Lond) 2012; **7**: 1017-1028 [PMID: 22348271 DOI: 10.2217/nnm.11.179]

47 **Korin N**, Kanapathipillai M, Matthews BD, Crescente M, Brill A, Mammoto T, Ghosh K, Jurek S, Bencherif SA, Bhatta D, Coskun AU, Feldman CL, Wagner DD, Ingber DE. Shear-activated nanotherapeutics for drug targeting to obstructed blood vessels. *Science* 2012; **337**: 738-742 [PMID: 22767894 DOI: 10.1126/science.1217815]

48 **Cohen AT**, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007; **98**: 756-764 [PMID: 17938798 DOI: 10.1160/TH07-03-0212]

49 **Jin HJ**, Zhang H, Sun ML, Zhang BG, Zhang JW. Urokinase-coated chitosan nanoparticles for thrombolytic therapy: preparation and pharmacodynamics in vivo. *J Thromb Thrombolysis* 2013; **36**: 458-468 [PMID: 23728739 DOI: 10.1007/s11239-013-0951-7]

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EDITORIAL

Reduction of radiation exposure in catheter ablation of atrial fibrillation: Lesson learned

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Abstract

Over the last decades, the concern for the radiation injury hazard to the patients and the professional staff has increased in the medical community. Since there is no magnitude of radiation exposure that is known to be completely safe, the use of ionizing radiation during medical diagnostic or interventional procedures should be as low as reasonably achievable (ALARA principle). Nevertheless, in cardiovascular medicine, radiation exposure for coronary percutaneous interventions or catheter ablation of cardiac arrhythmias may be high: for ablation of a complex arrhythmia, such as atrial fibrillation, the mean dose can be > 15 mSv and in some cases > 50 mSv. In interventional electrophysiology, although fluoroscopy has been widely used since the beginning to navigate catheters in the heart and the vessels and to monitor their position, the procedure is not based on fluoroscopic imaging. Therefore, non-fluoroscopic three-dimensional systems can be used to navigate electrophysiology catheters in the heart with no or minimal use of fluoroscopy. Although zero-fluoroscopy procedures are feasible in limited series, there may be difficulties in using no fluoroscopy on a routine basis. Currently, a significant reduction in radiation exposure towards near zero-fluoroscopy procedures seems a simpler task to achieve, especially in ablation of complex arrhythmias, such as atrial fibrillation. The data reported in the literature suggest the following three considerations. First, the use of the non-fluoroscopic systems is associated with a consistent reduction in radiation exposure in multiple centers: the more sophisticated and reliable this technology is, the higher the reduction in radiation exposure. Second, the use of these systems does not automatically lead to reduction of radiation exposure, but an optimized workflow should be developed and adopted for a safe non-fluoroscopic navigation of catheters. Third, at any level of expertise, there is a specific learning curve for the operators in the non-fluoroscopic manipulation of catheters; however, the learning curve is shorter for more experienced operators compared to less experienced operators.

Key words: Catheter ablation; Atrial fibrillation; Radiation exposure; Fluoroscopy time; Dose area product; Electro-anatomic mapping

Core tip: After 25 years from the formulation of the ALARA principle, the awareness of the potential hazard related to radiation exposure has greatly increased in medicine. Non-fluoroscopic three-dimensional systems, introduced in interventional electrophysiology to support complex procedures, have the potential to significantly decrease the use of fluoroscopy. In interventional electrophysiology, the clinical perspective is to perform procedures with minimal use of fluoroscopy without endangering the safety and efficacy. However, to achieve this task the use of the non-fluoroscopic system has to be optimized and a learning curve is necessary even for operators experienced in fluoroscopy-based electrophysiology.

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NEED FOR REDUCTION OF RADIATION EXPOSURE IN ELECTROPHYSIOLOGY PROCEDURES

Over the last years, the awareness of the risk related to the use of ionizing radiation in medicine has progressively increased. Cardiac imaging procedures lead to substantial radiation exposure in many patients: in a population-based analysis[1], the median cumulative effective dose over 3 years was 15.6 mSv and, among patients receiving a high annual dose (> 20-50 mSv), repeat cardiac catheterization procedures are the largest contributors to the radiation dose. The potential risks related to this radiation exposure are expected to be vastly outweighed by the benefits, especially if the procedure is appropriately justified and carefully optimized[2]. Although it is difficult to assess the consequences of the deterministic (dose-dependent) and stochastic (non dose-dependent) effects for the exposure to low-dose ionizing radiations used in cardiovascular imaging, the estimate of lifetime additional risk of cancer spans between 1/2000 and 1/1000 per single cardiovascular procedure[3]. It should be also taken into account that several patients undergo repeat procedures and that a younger patient population is more sensitive to the induction of cancer than an older patient population[4]. Similarly, the risk related to radiation exposure is not negligible for the medical staff. Noteworthy, according to a survey undertaken in Tuscany, Italy[5], interventional cardiologists and electrophysiologists represent more than 60% of the medical staff receiving the highest annual radiation exposure (> 6 mSv), with no statistically significant difference between physicians and nurses/technicians. This radiation exposure is by far greater than the one of the urologists, radiologists, and personnel of nuclear medicine. Moreover, according to the same source[5], the median lifetime professional exposure is 54 mSv, leading to an estimate lifetime attributable risk of cancer of 1 out of 200.

A decade ago, a document[6] endorsed by the main American scientific societies in cardiovascular medicine was published. This document states the clinical competence required for physicians performing fluoroscopically-guided invasive cardiovascular procedures to optimize patient safety and image quality. Importantly, it also highlights the ALARA principle, previously proposed by the United States National Council on Radiation Protection and Measurements[7]: due to both the stochastic and deterministic effect of radiation, there is no magnitude of radiation exposure that is known to be completely safe and, therefore, the use of ionizing radiations should be As Low As Reasonably Achievable. This principle confers to physicians the responsibility for reducing as much as possible the dose of radiation during cardiovascular procedures, in order to minimize the radiation injury hazard to the patients, to the professional staff and to themselves. The dose delivered to the patient depends on the following three factors: (1) type and setting of the X-ray equipment; (2) patient size; and (3) physician conduct. Consequently, all these three factors should be considered and optimized to comply with the ALARA principle. Importantly, opposite to what is commonly thought, fluoroscopy time poorly expresses the dose delivered to the patient. In fact, this value only reflects the operator's attitude to use radiation during a given procedure. Moreover, the same value of fluoroscopy time may correspond to a very different radiation exposure, depending on the predominant use of low-dose fluoroscopy or high-dose cine loop acquisition. Therefore, a reliable surrogate measurement for the total amount of X-ray energy delivered to the patient is the dose-area product (DAP), expressed usually in Gy·cm^2 and automatically measured by X-ray systems[6].

In the real world, after the dissemination of the ALARA principle, the process of optimization is still ongoing. Optimization depends on several factors, some of which are difficult to identify and control. Considering again the data by Chen *et al*[1], based on a population enrolled between 2005 and 2007, after the ALARA principle was diffused, percutaneous coronary interventions or electrophysiologic procedures were the main determinants of radiation exposure in the population receiving the highest radiation dose (> 20 mSv). As mentioned above, one of the determinants of the dose to the patient is the physician's conduct, which may be very much dependent on the physician's experience in a given procedure. In fact, in the very early phase of a physician's learning curve, the workflow can be far from being optimized and this can result in an excessive use of fluoroscopy. In this context, newer methodologies of teaching and learning can be effectively used. One small study performed in our

center[8] shows that the training implemented by a high-fidelity hybrid simulator reduces from 10 to 5 min, on average ($P < 0.0001$), the fluoroscopy time per patient spent by fellows novice in electrophysiology to position catheters in the conventional sites at the beginning of the procedure. In the future, if this or similar training modalities are not considered, we may face a new paradox: while the more experienced operators minimize radiation exposure in complex procedures using established techniques and technologies, the less experienced physicians use a higher dose for a standard and relatively simple procedure.

Recently, the European Society of Cardiology published two position papers on the appropriate and justified use of medical radiation in cardiovascular imaging[9] and on the practical ways to reduce radiation dose for patients and staff during electrophysiology procedures[10]. Focusing on the field of interventional electrophysiology, these papers report the radiation dose to the patients for electrophysiology procedures. This dose may vary from 3.2 mSv for a simple diagnostic electrophysiology study to a higher value for complex procedures, such as atrial fibrillation ablation, for which the median dose is 16.6 mSv, ranging from 6.6 to 59.6 mSv[10]. Another review of 17 studies, 12 of them published after the year 2000, reports an effective dose even higher (20.3 mSv) for catheter ablation of cardiac arrhythmias, in general, including ablation of less complex arrhythmias[11]. As suggested by the consensus document[10], this situation still requires further improvement, once optimization of X-ray equipment and shielding of the laboratory personnel are obtained. In fact, non-fluoroscopic three-dimensional systems, namely the Ensite-NavX (St.Jude Medical, United States) and the CARTO (Biosense Webster, United States), widely used since the late nineties for ablation of complex arrhythmias, can be used effectively to reduce radiation exposure during electrophysiology procedures. In a randomized study[12], the use of these systems for catheter ablation of cardiac arrhythmias reduced X-ray exposure with a similar efficacy and safety compared to the conventional approach. However, it should be highlighted that the use of these systems does not *per se* reduce radiation exposure, but the operators should develop procedural workflows to rely on non-fluoroscopic guidance as much as possible without compromising safety[10]. Especially for complex left atrial procedure during which the operator may face different anatomic variants, integration in these systems of pre-acquired three-dimensional imaging from computed tomography or magnetic resonance scan has the potential to drastically reduce the radiation exposure during the procedure[9].

The following sections will focus on reducing radiation exposure in catheter ablation of atrial fibrillation. This is an increasingly used procedure especially in patients with paroxysmal forms and, moreover, the use of fluoroscopy in such a complex and demanding procedure can be high. Therefore, reduction of radiation exposure in this procedure is expected to increase the net benefit of the procedure, minimizing the risks, which can be also related to the radiation exposure especially in case of repeat procedures.

ZERO OR NEAR-ZERO FLUOROSCOPY FOR ATRIAL FIBRILLATION ABLATION?

Unlike percutaneous coronary interventions, electrophysiologic procedures are based on recording and interpretation of intracavitary electrograms. Therefore, although fluoroscopy is very useful to maneuver and check the position of catheters, imaging based on ionizing radiations is not an integral part of the electrophysiologic procedure. In fact, ablation of various types of supraventricular and ventricular tachycardia with no use of fluoroscopy is feasible both in children[13-18] and adults[19-22] using non-fluoroscopic three-dimensional systems. Also a complex procedure, such as pulmonary vein isolation to treat atrial fibrillation, is feasible with no use of fluoroscopy[23,24]. Although these studies certainly demonstrate the feasibility of zero-fluoroscopy procedures, this issue deserves several considerations, especially in the case of complex procedures such as atrial fibrillation ablation. First, the majority of the reported series and in particular those on catheter ablation of atrial fibrillation are small and from very experienced centers. Even for senior electrophysiologists there may be a learning curve in the transition from fluoroscopically based procedures to zero-fluoroscopy procedures[17]. Second, even in the best scenario of published data on procedure planned to be with no fluoroscopy, very limited radiations are used in some cases[23] to assist a part of the procedure. Extrapolating these data to a wider population, it is unlikely that in the near future electrophysiologists will be able to work in laboratories not equipped with X-ray systems. Therefore, the zero-fluoroscopy strategy does not seem to bring any benefit in term of laboratory costs. Third, in ablation of atrial fibrillation with no fluoroscopy, some technologies, which require specific expertise and add costs in centers in which they are not routinely used, become necessary. In fact, to safely navigate catheters in the heart with no fluoroscopy, intracardiac ultrasounds is mandatory and imaging integration with pre-acquired computed tomography or magnetic resonance imaging very useful to obtain a high resolution anatomy of the left atrium and pulmonary veins[23,24]. The use of the recently introduced contact force sensing technology should be also considered mandatory to avoid excessive tissue/catheter contact when catheters are maneuvered with no fluoroscopy[22]. Fourth, the workflow of a zero-fluoroscopy procedure requires accurate cardiac chamber reconstruction before non-fluoroscopic catheter navigation. This can be done correctly only by experienced operators and, in any case, may significantly prolong the procedure duration, especially at the beginning of the specific learning curve in zero-

Table 1 Techniques and technologies for catheter ablation of atrial fibrillation in the four patient cohorts considered in our center

	1st cohort	2nd cohort	3rd cohort	4th cohort
No. of patients	30	30	30	30
Procedure technique	Double TSP-C Circular mapping catheter Imaging integration (CT scan)	Unchanged	Unchanged	Unchanged
NF technology	2nd generation NF 3-DS (CARTO XP)	3rd generation NF 3-DS (CARTO3)	Unchanged	CARTO3 + contact force sensing
Technology feature for NF use	NF visualization of the mapping/ablation catheter	NF visualization of all inserted catheter	Unchanged	Monitoring of the electrode/tissue contact added
NF 3-DS optimization	Yes	No	Yes (Table 2)	Yes (Table 2)
Timing	Last 30 cases with CARTO XP	First 30 cases with CARTO3	After 12 mo	After 12 mo

3-DS: Three dimensional system; CT: Computed tomography; NF: Non-fluoroscopic; TSP-C: Transseptal catheterization.

fluoroscopy procedures.

After these considerations, it can be concluded that zero-fluoroscopy procedures are a very interesting perspective for the future, but they are not common practice at present. Certainly, children and pregnant women are ideal candidates for zero-fluoroscopy catheter ablation, when other treatments fail or are not feasible. On the other hand, currently, every effort should be made by every operator to decrease as much as possible the use of radiation without endangering the procedure safety and efficacy until near-zero fluoroscopy procedures become routine.

LESSON LEARNED IN THE REDUCTION OF RADIATION EXPOSURE FOR ATRIAL FIBRILLATION ABLATION

Even in very experienced hands, catheter ablation of atrial fibrillation without a non-fluoroscopic three-dimensional system is associated with a fluoroscopy time of approximately 60 min[25] and, consequently, with a relatively high radiation exposure. However, as already mentioned[10], a non-fluoroscopic system without a workflow aimed at optimizing its use does not necessarily reduce the radiation exposure. In fact, in catheter ablation of atrial fibrillation, the sporadic use of non-fluoroscopic systems may paradoxically double the fluoroscopy time and radiation exposure when the system is used, due to the complexity of the procedure[26]. In a retrospective analysis[27] spanning 6 years (2004-2009) and including four cohorts of patients who showed comparable clinical characteristics and underwent catheter ablation of atrial fibrillation by using in a non-randomized way fluoroscopy or one of the non-fluoroscopic systems (Ensite NavX, CARTO XP, CARTO3), a third generation non-fluoroscopic system (CARTO 3) was associated with the shortest fluoroscopy time with no difference with the other 3 groups in term of procedural data and clinical outcomes. Although the reduction was statistically significant, the average fluoroscopy time using CARTO 3 in this study was still close to one hour (52 ± 21 min). This underlines the complexity of the variables that may determine the reduction of radiation exposure, which is not merely due to the use of a specific non-fluoroscopic system. Another study[28] further supports this concept. In this study, over six months, 120 patients were randomly assigned to use fluoroscopy only, a second generation (CARTO XP), or a third generation (CARTO3) non-fluoroscopic system to support catheter ablation of atrial fibrillation. The procedure was performed by operators with a specific experience in reduction of radiation exposure. While there was no difference in the clinical and anatomic variables among the three groups, the fluoroscopy time was shorter and less than 3 min for the whole procedure when the third generation non-fluoroscopic system was used with an optimized procedural workflow.

We evaluated the process of reduction of radiation exposure in catheter ablation of atrial fibrillation using a non-fluoroscopic three-dimensional electroanatomic system both in a single- and multicenter experience[29,30]. In our center, the procedural data of four cohorts of patients, sampled sequentially, were considered[29]. Each cohort included atrial fibrillation patients undergoing the first procedure of pulmonary vein isolation. The technologies and techniques used in each cohort are reported in Table 1. Among the four cohorts there was no significant difference in the clinical characteristics of the patients, in term of age, sex, body mass index, type and duration of atrial fibrillation, which reflects the homogeneous criteria used to select candidates for atrial fibrillation ablation in the considered time interval. The procedure was standardized as described elsewhere[31] and it was alternatively performed by two operators with a similar experience in atrial fibrillation ablation (> 400 procedures each), although the background in interventional electrophysiology was different (23 years *vs* 10 years, respectively). Importantly, the radiation exposure for the pre-procedure computed tomography scan was very low (< 1 mSv) due to an optimized acquisition protocol[31]. In the 3rd and 4th cohort, the use of a third generation non-fluoroscopic three-dimensional system was optimized by adopting the features listed in Table 2, including in the 4th cohort the recently introduced

Table 2 Features of the third generation non-fluoroscopic system CARTO 3 useful to minimize fluoroscopy during an electrophysiology procedure

Feature	Function
Imaging integration with pre-acquired CT or MRI image	Allows high resolution visualization of the LA and PVs; once registered in the system, the mapping/ablation catheter can be navigated with minimal use of fluoroscopy
Display in stable mode of the icon of the mapping/ablation catheter	Allows stable visualization of the mapping/ablation catheter on the system, similar to the one visualized on fluoroscopy
Colors on the distal part of the mapping/ablation catheter	Indicate the direction of the deflection of the distal part of the catheter
Catheter projection	Estimates the distance from the catheter tip to the surface of the electroanatomic map or to the surface of the CT/MRI image
Contact force sensing	Measures in grams the contact between the catheter tip and the tissue; used to avoid excessive contact during catheter manipulation and to optimize contact during ablation
Real time display of the circular mapping catheter	Allows real time visualization of the circular mapping catheter during positioning into the PVs
Highlight of the circular mapping catheter electrodes	Identify the position of the electrodes of the circular mapping catheter; used to identify the site of a conducting gap during circumferential PV ablation
Catheter snapshot	Shows a memorized position of a catheter (*e.g.*, circular mapping catheter); used to precisely re-navigated a previous catheter positioning

CT: Computed tomography; LA: Left atrium; MRI: Magnetic resonance imaging; PV: Pulmonary vein.

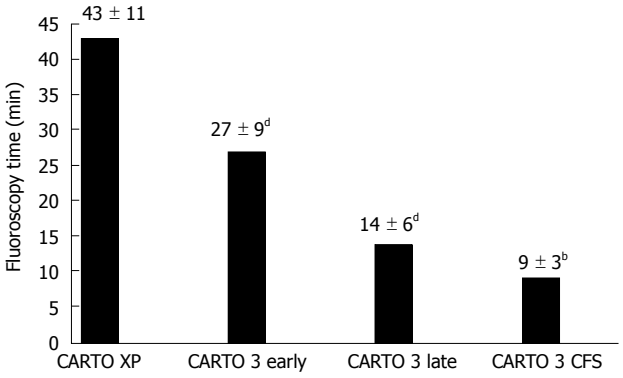

Figure 1 Histogram of fluoroscopy time (in minutes) for the whole procedure of pulmonary vein isolation in four cohorts of patients with atrial fibrillation, using the non-fluoroscopic CARTO system with progressively new technologies and protocols. There is a progressive and significant reduction in fluoroscopy time, but the greatest percent reduction (-48%) is observed between the second and third cohort, CARTO 3 early *vs* CARTO 3 late. In these two cohorts the technology was the same, but in the second one the system was used with an optimized protocol to reduce fluoroscopy. $^{b}P < 0.001$ *vs* the previous cohort; $^{d}P < 0.0001$ *vs* the previous cohort. CFS: Contact force sensing.

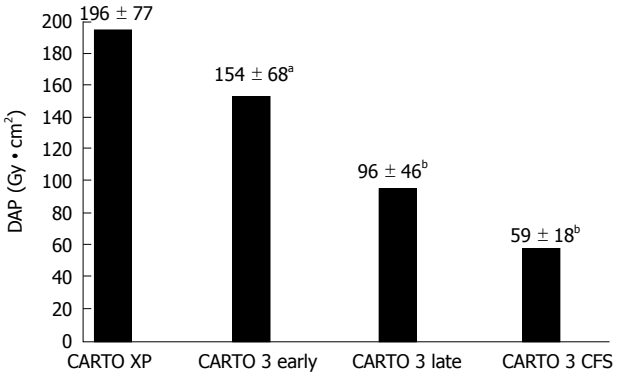

Figure 2 Histogram of dose area product values (in Gy•cm^2) for the whole procedure of pulmonary vein isolation in the same cohorts shown in Figure 1. As in Figure 1, there is a progressive and significant reduction in radiation exposure, expressed by the dose area product value. $^{a}P < 0.05$ *vs* the previous cohort; $^{b}P < 0.0001$ *vs* the previous cohort. DAP: Dose area product; CFS: Contact force sensing.

contact force sensing technology[32]. This was mainly used to avoid excessive contact force between the tip of the mapping/ablation catheter and the endocardium when the catheter was advanced non-fluoroscopically. Importantly, during non-fluoroscopic navigation of the catheter, its position was continuously monitored on the CARTO, to avoid events at risk for complications, such as entrapment of the circular mapping catheter in the mitral valve apparatus. While the procedural data, in term of procedure duration, number of pulmonary vein isolated, radiofrequency energy time, acute success and complication, was not significantly different among the four cohorts, there was a progressive decrease in fluoroscopy time and DAP values, as shown in Figures 1 and 2, respectively. Sub-analyzing data per operator, there are interesting findings when the 1st cohort is compared to the 2nd and the 2nd to the 3rd. In the first comparison, the more experienced operator obtained a 46% reduction (from 41 ± 9 to 22 ± 6 min, on average; $P < 0.0001$) in fluoroscopy time compared to only a 22% reduction (from 43 ± 13 to 33 ± 9 min, on average; $P = 0.0012$) obtained by the less experienced operator. Interestingly, an opposite phenomenon was observed in the second comparison: the more experienced operator, who had already obtained a greater reduction in the use of fluoroscopy, had a 36% reduction in fluoroscopy time (from 22 ± 6 min to 14 ± 5 min, on average; $P < 0.001$), definitely smaller than the 54% reduction obtained by the second operator (from 33 ± 9 min to 15 ± 7 min, on average, $P < 0.001$).

These data deserve two considerations, on the technology and the learning curve, respectively. First, the ability to reduce significantly radiation exposure towards a near zero-fluoroscopy procedure depends on the type and quality of the non-fluoroscopic system. A third generation non-fluoroscopic system, able to reliably visualize all the catheters inserted in the heart,

allows catheter manipulation with minimal or no use of fluoroscopy leading to an immediate improvement in radiation exposure compared to the older system. This was confirmed in the multicentric study in 240 consecutive patients undergoing catheter ablation of atrial fibrillation[30]. In this study, the average fluoroscopy time decreased from 26 ± 15 min to 16 ± 12 min ($P < 0.001$) and the positive effect of adopting the third generation system was significant in all the participating centers. The importance of the technology is further confirmed by the observation in our center of a still significant reduction in radiation exposure when the newer contact force sensing technology was introduced. The second consideration is on the need for a specific learning curve. Although in the multicenter study[30] the reduction in the use of fluoroscopy is observed in all centers, the percent reduction spans from 25% to 56% among centers. This is likely to be related to a specific learning curve in reduction of radiation exposure. In fact, considering again the data from our center, a more experienced electrophysiologist may exhibit a shorter learning curve in the reduction of radiation exposure, while a less experienced one eventually reaches the same level of ability in non-fluoroscopic maneuvering of catheters after a longer learning curve.

CONCLUSION

Over the last years, the awareness of the radiation injury hazard to the patients and the professional staff has greatly increased. Reduction in the radiation exposure in a complex electrophysiology procedure, such as atrial fibrillation ablation, should be considered. This is an increasingly used procedure with usually longer fluoroscopy times. Therefore, the decrease in radiation exposure is expected to improve the net benefit of the procedure for the patient and to minimize the radiation injury hazard for the professional staff. The lesson learned so far tells us that sophisticated technologies have to combine with a specific know-how to achieve this task. In fact, non-fluoroscopic three-dimensional systems with their constant updating in the technology content have a key role, but minimization in the use of radiations is obtained if these technologies are used with an optimized protocol and after a specific operators' learning curve. This may last several months and be longer for less experience operators.

REFERENCES

1 **Chen J**, Einstein AJ, Fazel R, Krumholz HM, Wang Y, Ross JS, Ting HH, Shah ND, Nasir K, Nallamothu BK. Cumulative exposure to ionizing radiation from diagnostic and therapeutic cardiac imaging procedures: a population-based analysis. *J Am Coll Cardiol* 2010; **56**: 702-711 [PMID: 20619569 DOI: 10.1016/j.jacc2010.05.014]

2 **Budoff MJ**, Gupta M. Radiation exposure from cardiac imaging procedures: do the risks outweigh the benefits? *J Am Coll Cardiol* 2010; **56**: 712-714 [PMID: 20619568 DOI: 10.1016/j.jacc.2010.03.055]

3 **Picano E**. Informed consent and communication of risk from radiological and nuclear medicine examinations: how to escape from a communication inferno. *BMJ* 2004; **329**: 849-851 [PMID: 15472270 DOI: 10.1136/bmj329.7470.849]

4 **Hall EJ**. Lessons we have learned from our children: cancer risks from diagnostic radiology. *Pediatr Radiol* 2002; **32**: 700-706 [PMID: 12244457 DOI: 10.1007/s00247-002-0774-8]

5 **Venneri L**, Rossi F, Botto N, Andreassi MG, Salcone N, Emad A, Lazzeri M, Gori C, Vano E, Picano E. Cancer risk from professional exposure in staff working in cardiac catheterization laboratory: insights from the National Research Council's Biological Effects of Ionizing Radiation VII Report. *Am Heart J* 2009; **157**: 118-124 [PMID: 19081407 DOI: 10.1016/j.ahj.2008.08.009]

6 **Hirshfeld JW**, Balter S, Brinker JA, Kern MJ, Klein LW, Lindsay BD, Tommaso CL, Tracy CM, Wagner LK, Creager MA, Elnicki M, Hirshfeld JW, Lorell BH, Rodgers GP, Tracy CM, Weitz HH. ACCF/AHA/HRS/SCAI clinical competence statement on physician knowledge to optimize patient safety and image quality in fluoroscopically guided invasive cardiovascular procedures. A report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training. *J Am Coll Cardiol* 2004; **44**: 2259-2282 [PMID: 15582335 DOI: 10.1016/j.jacc.2004.10.014]

7 National Council on Radiation Protection and Measurements. Implementation of the principle of as low as reasonably achievable (ALARA) for medical and dental personnel. Bethesda (MD): NRCP report no.107. Available from: URL: http://www.ncrponline.org/Publications/Press_Releases/107press.html

8 **De Ponti R**, Marazzi R, Doni LA, Tamborini C, Ghiringhelli S, Salerno-Uriarte JA. Simulator training reduces radiation exposure and improves trainees' performance in placing electrophysiologic catheters during patient-based procedures. *Heart Rhythm* 2012; **9**: 1280-1285 [PMID: 22516184 DOI: 10.1016/j.hrthm.2012.04.015]

9 **Picano E**, Vañó E, Rehani MM, Cuocolo A, Mont L, Bodi V, Bar O, Maccia C, Pierard L, Sicari R, Plein S, Mahrholdt H, Lancellotti P, Knuuti J, Heidbuchel H, Di Mario C, Badano LP. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. *Eur Heart J* 2014; **35**: 665-672 [PMID: 24401558 DOI: 10.1093/eurheart/eht394]

10 **Heidbuchel H**, Wittkampf FH, Vano E, Ernst S, Schilling R, Picano E, Mont L, Jais P, de Bono J, Piorkowski C, Saad E, Femenia F. Practical ways to reduce radiation dose for patients and staff during device implantations and electrophysiological procedures. *Europace* 2014; **16**: 946-964 [PMID: 24792380 DOI: 10.1093/europace/eut409]

11 **Pantos I**, Patatoukas G, Katritsis DG, Efstathopoulos E. Patient radiation doses in interventional cardiology procedures. *Curr Cardiol Rev* 2009; **5**: 1-11 [PMID: 20066141 DOI: 10.2174/157340309787048059]

12 **Earley MJ**, Showkathali R, Alzetani M, Kistler PM, Gupta D, Abrams DJ, Horrocks JA, Harris SJ, Sporton SC, Schilling RJ. Radiofrequency ablation of arrhythmias guided by non-fluoroscopic catheter location: a prospective randomized trial. *Eur Heart J* 2006; **27**: 1223-1229 [PMID: 16613932 DOI: 10.1093/eurheartj/ehi834]

13 **Drago F**, Silvetti MS, Di Pino A, Grutter G, Bevilacqua M, Leibovich S. Exclusion of fluoroscopy during ablation treatment of right accessory pathway in children. *J Cardiovasc Electrophysiol* 2002; **13**: 778-782 [PMID: 12212697 DOI: 10.1046/j.1540-8167.2002.00778.x]

14 **Smith G**, Clark JM. Elimination of fluoroscopy use in a pediatric electrophysiology laboratory utilizing three-dimensional mapping. *Pacing Clin Electrophysiol* 2007; **30**: 510-518 [PMID: 17437575 DOI: 10.1111/j.1540-8159.2007.701.x]

15 **Clark J**, Bockoven JR, Lane J, Patel CR, Smith G. Use of three-dimensional catheter guidance and trans-esophageal echocardiography to eliminate fluoroscopy in catheter ablation of left-sided accessory pathways. *Pacing Clin Electrophysiol* 2008; **31**: 283-289 [PMID: 18307622 DOI: 10.1111/j.1540-8159.2008.00987.x]

16 **Miyake CY**, Mah DY, Atallah J, Oikle HP, Melgar ML, Alexander ME, Berul CI, Cecchin F, Walsh EP, Triedman JK. Nonfluoroscopic imaging systems reduce radiation exposure in children undergoing

ablation of supraventricular tachycardia. *Heart Rhythm* 2011; **8**: 519-525 [PMID: 21167315 DOI: 10.1016/j.hrthm.2010.12.022]
17 **Gist K**, Tigges C, Smith G, Clark J. Learning curve for zero-fluoroscopy catheter ablation of AVNRT: early versus late experience. *Pacing Clin Electrophysiol* 2011; **34**: 264-268 [PMID: 21070259 DOI: 10.1111/j.1540-8159.2010.02952.x]
18 **Tuzcu V**. Significant reduction of fluoroscopy in pediatric catheter ablation procedures: long-term experience from a single center. *Pacing Clin Electrophysiol* 2012; **35**: 1067-1073 [PMID: 22817263 DOI: 10.1111/j.1540-8159.2012.03472.x]
19 **Alvarez M**, Tercedor L, Almansa I, Ros N, Galdeano RS, Burillo F, Santiago P, Peñas R. Safety and feasibility of catheter ablation for atrioventricular nodal re-entrant tachycardia without fluoroscopic guidance. *Heart Rhythm* 2009; **6**: 1714-1720 [PMID: 19959117 DOI: 10.1016/j.hrthm.2009.08.037]
20 **Casella M**, Pelargonio G, Dello Russo A, Riva S, Bartoletti S, Santangeli P, Scarà A, Sanna T, Proietti R, Di Biase L, Gallinghouse GJ, Narducci ML, Sisto L, Bellocci F, Natale A, Tondo C. "Near-zero" fluoroscopic exposure in supraventricular arrhythmia ablation using the EnSite NavX™ mapping system: personal experience and review of the literature. *J Interv Card Electrophysiol* 2011; **31**: 109-118 [PMID: 21365263 DOI: 10.1007/s10840-011-9553-5]
21 **Giaccardi M**, Chiodi L, Del Rosso A, Colella A. 'Zero' fluoroscopic exposure for ventricular tachycardia ablation in a patient with situs viscerum inversus totalis. *Europace* 2012; **14**: 449-450 [PMID: 22089170 DOI: 10.1093/europace/eur359]
22 **Kerst G**, Weig HJ, Weretka S, Seizer P, Hofbeck M, Gawaz M, Schreieck J. Contact force-controlled zero-fluoroscopy catheter ablation of right-sided and left atrial arrhythmia substrates. *Heart Rhythm* 2012; **9**: 709-714 [PMID: 22222276 DOI: 10.1016/j.hrthm.2011.12.025]
23 **Ferguson JD**, Helms A, Mangrum JM, Mahapatra S, Mason P, Bilchick K, McDaniel G, Wiggins D, DiMarco JP. Catheter ablation of atrial fibrillation without fluoroscopy using intracardiac echocardiography and electroanatomic mapping. *Circ Arrhythm Electrophysiol* 2009; **2**: 611-619 [PMID: 20009075 DOI: 10.1161/CIRCEP.109.872093]
24 **Reddy VY**, Morales G, Ahmed H, Neuzil P, Dukkipati S, Kim S, Clemens J, D'Avila A. Catheter ablation of atrial fibrillation without the use of fluoroscopy. *Heart Rhythm* 2010; **7**: 1644-1653 [PMID: 20637313 DOI: 10.1016/j.hrthm.2010.07.011]
25 **Macle L**, Weerasooriya R, Jais P, Scavee C, Raybaud F, Choi KJ, Hocini M, Clementy J, Haissaguerre M. Radiation exposure during radiofrequency catheter ablation for atrial fibrillation. *Pacing Clin Electrophysiol* 2003; **26**: 288-291 [PMID: 12687830 DOI: 10.1046/j.1460-9592.2003.00034.x]
26 **Smith IR**, Rivers JT, Hayes J, Stafford W, Codd C. Reassessment of radiation risks from electrophysiology procedures compared to coronary angiography. *Heart Lung Circ* 2009; **18**: 191-199 [PMID: 19119073 DOI: 10.1016/j.hlc.2008.10.006]
27 **Khaykin Y**, Oosthuizen R, Zarnett L, Wulffhart ZA, Whaley B, Hill C, Giewercer D, Verma A. CARTO-guided vs. NavX-guided pulmonary vein antrum isolation and pulmonary vein antrum isolation performed without 3-D mapping: effect of the 3-D mapping system on procedure duration and fluoroscopy time. *J Interv Card Electrophysiol* 2011; **30**: 233-240 [PMID: 21253840 DOI: 10.1007/s10840-010-9538-9]
28 **Scaglione M**, Biasco L, Caponi D, Anselmino M, Negro A, Di Donna P, Corleto A, Montefusco A, Gaita F. Visualization of multiple catheters with electroanatomical mapping reduces X-ray exposure during atrial fibrillation ablation. *Europace* 2011; **13**: 955-962 [PMID: 21421574 DOI: 10.1093/europace/eur062]
29 **De Ponti R**, Marazzi R, Doni LA, Mameli S, Salerno-Uriarte JA. Learning curve of radiation exposure using a three-dimensional electroanatomic system for atrial fibrillation: a single center experience. *J Arrhythm* 2012; **28** (abstract supplemet): 597
30 **Stabile G**, Scaglione M, del Greco M, De Ponti R, Bongiorni MG, Zoppo F, Soldati E, Marazzi R, Marini M, Gaita F, Iuliano A, Bertaglia E. Reduced fluoroscopy exposure during ablation of atrial fibrillation using a novel electroanatomical navigation system: a multicentre experience. *Europace* 2012; **14**: 60-65 [PMID: 21893511 DOI: 10.1093/europace/eur271]
31 **De Ponti R**, Marazzi R, Lumia D, Picciolo G, Biddau R, Fugazzola C, Salerno-Uriarte JA. Role of three-dimensional imaging integration in atrial fibrillation ablation. *World J Cardiol* 2010; **2**: 215-222 [PMID: 21160587 DOI: 10.4330/wjc.v2.i8.215]
32 **Nakagawa H**, Kautzner J, Natale A, Peichl P, Cihak R, Wichterle D, Ikeda A, Santangeli P, Di Biase L, Jackman WM. Locations of high contact force during left atrial mapping in atrial fibrillation patients: electrogram amplitude and impedance are poor predictors of electrode-tissue contact force for ablation of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2013; **6**: 746-753 [PMID: 23873143 DOI: 10.1161/CIRCEP.113.978320]

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EDITORIAL

Glycated hemoglobin and its spinoffs: Cardiovascular disease markers or risk factors?

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Abstract

Atherosclerosis is a major complication of diabetes, increasing the risk of cardiovascular related morbidities and mortalities. The hallmark of diabetes is hyperglycemia which duration is best predicted by elevated glycated haemoglobin A_{1c} (HbA_{1c}) levels. Diabetic complications are usually attributed to oxidative stress associated with glycation of major structural and functional proteins. This non-enzymatic glycation of long lived proteins such as collagen, albumin, fibrinogen, liver enzymes and globulins result in the formation of early and advanced glycation end products (AGEs) associated with the production of myriads of free radicles and oxidants that have detrimental effects leading to diabetic complications. AGEs have been extensively discussed in the literature as etiological factors in the advancement of atherogenic events. Mechanisms described include the effects of glycation on protein structure and function that lead to defective receptor binding, impairment of immune system and enzyme function and alteration of basement membrane structural integrity. Hemoglobin (Hb) is a major circulating protein susceptible to glycation. Glycated Hb, namely HbA_{1c} is used as a useful tool in the diagnosis of diabetes progression. Many studies have shown strong positive associations between elevated HbA_{1c} levels and existing cardiovascular disease and major risk factors. Also, several studies presented HbA_{1c} as an independent predictor of cardiovascular risk. In spite of extensive reports on positive associations, limited evidence is available considering the role of glycated Hb in the etiology of atherosclerosis. This editorial highlights potential mechanisms by which glycated hemoglobin may contribute, as a causative factor, to the progression of atherosclerosis in diabetics.

Key words: Glycated hemoglobin; Glycoxidative stress; Advanced glycation end products; Atherosclerosis; Diabetes mellitus

Core tip: Glycated hemoglobin is a useful marker for the diagnosis of diabetes progression. Many studies present glycated haemoglobin (HbA_{1c}) as an independent predictor of cardiovascular risk in diabetics. Although haemoglobin (Hb) is a major circulating protein, limited

information is available about the role of glycated Hb as such in the etiology of atherosclerosis. This editorial highlights potential mechanisms by which glycated hemoglobin may contribute, as a causative factor, to the progression of atherosclerosis in diabetics.

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EDITORIAL

Abundant evidence exists that patients with diabetes mellitus have an increased risk of atherosclerosis and are more vulnerable to its progression into cardiovascular disease[1]. Several mechanisms were proposed to describe the pathogenesis of atherosclerosis in diabetic patients. Vascular endothelial cell damage, as a result of blood flow shear stress, increased blood viscosity and oxidative stress were described in several studies[1-4]. The chronic hyperglycemic state in diabetes creates an environment of oxidative stress manifested as a glycoxidative state[5]. This state is characterized by the accumulation of glycated proteins that are further modified into advanced glycation end products (AGEs). The discovery of AGEs dates back to 1912 when Louis-Camille Maillard originally observed a chemical reaction between amino acids and reducing sugars that gave browned foods their desirable flavor[6]. Human proteins normally undergo spontaneous non-enzymatic glycation reaction forming low levels of glycated products[7]. However, chronic exposure to abnormally high glucose levels leads to further modifications. The aldehyde group of the glucose molecule combines with the amino group of a lysine molecule in a protein to form a Schiff base which is a double bond between the carbon atom of the glucose and the nitrogen atom of lysine. The Schiff bases form Amadori products that undergo further molecular rearrangements producing advanced glycated end products AGEs. The formation of AGEs is accompanied by the release of myriads of oxidants and free radicals that cause oxidative damage in the cells and extracellular matrix. Subsequent degradation of AGEs produces more reactive oxidant species and protein reactive aldehydes that contribute to further macromolecular alterations[1,8,9]. In diabetes, long-lived proteins such as collagen, elastin and many enzymes are affected by advanced glycation which disrupts their structure and function[10]. Accumulation of AGE products contribute to a variety of vascular complications through the formation of cross-links between molecules leading to hardening of the vascular extracellular matrix (ECM) and increasing vascular permeability[9-11]. Modification of the extracellular matrix by AGEs traps cholesterol rich lipoproteins promoting their oxidation and stimulates an inflammatory response that accelerates plaque formation and advancement of the atherogenic process. Evidence of the formation of AGEs and their detrimental role in the pathogenesis and development of cardiovascular disease is extensively reported in the literature[10-13].

GLYCATED HEMOGLOBIN AS A DIAGNOSTIC MARKER AND ADVANCED GLYCATION PRODUCT

The extent and duration of hyperglycemia is best predicted by increased levels of glycated hemoglobin (glycated Hb) of which HbA_{1c} is considered a reliable marker[14,15]. HbA_{1c} in the medical literature is commonly described as a useful measure to reflect the duration of increased blood glucose levels up to several months[14]. Numerous studies have shown positive associations between elevated HbA_{1c} levels and cardiovascular disease including acute coronary syndrome, acute myocardial infarction and heart failure[15,16]. Large prospective cohort studies showed that HbA_{1c} is not only a diagnostic marker of diabetes progression, but also an independent cardiovascular risk predictor[17]. As mentioned earlier, prolonged sugar exposure produces early and AGEs affecting different proteins. A major example of early glycated proteins is HbA_{1c} which is further modified, through a series of reactions, into Hb-AGE[18]. Under normal conditions Hb-AGE constitutes 0.42% of circulating Hb levels which increases to 0.75% in diabetic subjects[19]. In spite of extensive reports showing positive associations between increased HbA_{1c} levels and cardiovascular risk in diabetics, the role of HbA_{1c} and Hb-AGE as potential etiological culprits in diabetic disease progression has been rarely discussed. This editorial highlights mechanisms by which glycated Hb may contribute, as a causative factor, to the initiation and development of atherosclerosis in diabetics.

HB GLYCATION ACCENTUATES INTRACELLULAR OXIDATIVE STRESS AND INCREASES ERYTHROCYTE FRAGILITY

Besides albumin, hemoglobin comprises a major fraction of circulating proteins that are susceptible to early and advanced glycation events. Glycation is accelerated in diabetics[11] where glucose uptake by erythrocytes is insulin independent and highly uncontrolled. Furthermore, glycated Hb is more readily oxidized and degraded by erythrocyte proteolytic enzymes than unglycated Hb[20,21] enhancing oxidative stress by increasing the release of heme and free iron in association with free radicles[22-25]. The released ferrous iron (II) reacts with hydrogen peroxide *via* the

Fenton reaction forming ferric iron (II) and hydroxyl radicals[26]. These reactive species contribute to further oxidative stress damaging lipids and proteins that alter cell membrane properties and lead to increased erythrocyte fragility[27,28]. High exposure to oxygen during gas transport render erythrocytes even more vulnerable to oxidative damage. However, damage is normally prevented by anti-oxidant factors that maintain a balanced intracellular oxidation status. This balanced environment maintains an intact Hb structure which itself exerts a stabilizing effect on erythrocyte membrane structure. When Hb structure is altered due to persistent glyco-oxidative stress, Hb becomes more susceptible to degradation decreasing the life span of erythrocytes. Studies have shown a decreased life span of 6.9 d for 1% increase in glycated Hb levels[29].

HB GLYCATION AFFECTS BLOOD VISCOSITY AND CONTRIBUTES TO ENDOTHELIAL INFLAMMATION AND VASCULAR DYSFUNCTION

Intracellular glyco-oxidative stress may contribute to vascular endothelial damage through several mechanisms: (1) accumulation of intracellular free radicals alters erythrocyte membrane properties leading to erythrocyte aggregation, increased blood viscosity and impaired blood flow. Shear stress, due to thicker abrasive blood consistency, affecting the vascular endothelium and triggering an inflammatory response that contribute to subsequent atherogenic events[3,4,27,28,30]; (2) buildup of free radicles promotes the oxidation of ferrous Hb (Hb-Fe^{2+}) into ferric Hb (Hb-Fe^{3+}) (methemoglobin), which is further modified, through several oxidation steps, into ferryl hemoglobin (Hb-Fe^{3+}/Fe^{4+}). The ferryl iron (Fe^{4+}) is unstable and regains the Fe^{3+} state by reacting with specific amino acids in hemoglobin forming covalently cross-linked Hb multimers[31]. The altered Hb structure promotes cellular damage and releases ferryl Hb into the subendothelial matrix. Silva *et al*[32] demonstrated that ferryl Hb, rather than Hb, or methemoglobin, increased endothelial permeability and production of pro-inflammatory monocyte adhesion proteins that promote macrophage accumulation and a local inflammatory reaction preceding plaque formation; (3) Free Hb penetrates the vascular smooth muscle layer[33] and inactivates endothelium-dependent relaxation induced by acetylcholine[34] possibly through binding to nitric oxide (NO) which is a potent vasodilator which initiates vaso-relaxation in response to stimuli. Nitric oxide also inhibits formation of oxidized LDL[35] which detrimental to endothelial integrity. Inactivation of NO is a major marker of endothelial dysfunction manifested in impaired vasoactive responses[35]. Rodríguez-Mañas *et al*[36] demonstrated that highly glycosylated Hb inhibited nitric oxide mediated relaxation to a larger extent than low glycated and unglycated Hb. The authors suggested that Hb-AGEs may exacerbate this effect as abundant *in vitro* and *in vivo* evidence demonstrates that AGEs inhibit nitric oxide production and function[36]; and (4) Furthermore, accelerated degradation of erythrocytes releases heme which sensitizes endothelial cells to oxidative damage and promotes oxidation of endothelial proteins and low density lipoproteins (LDLs)[31].

Altogether, these adverse modifications trigger a proliferative inflammatory response in the subendothelial space which involves recruitment of a myriad of inflammatory and immune factors including monocytes, platelets, lymphocytes and increased production of various growth factors and cytokines such as IL-1 and TNF-α and adhesion molecules[37]. Oxidized LDL particles are subsequently scavenged by macrophages forming lipid rich foam cells that contribute to the formation of fatty streaks and subsequent build-up of plaque. As atherosclerotic plaque builds up, further insult to the endothelium activates a vicious cycle of inflammatory/oxidation events and further progression of atherosclerosis[38]. The list of endothelial mediators that contribute to this inflammatory/atherogenic process continues to grow. Interleukin-17 (IL-17), produced by T-helper cells, induces chemokines such as IL-6, IFN-γ and TNF-α to recruit monocytes and neutrophils to the site of inflammation. Recent evidence points to additional allergic/hypergic responses, induced by IL-17, which involve cytokines such as IL-8 and eotaxin believed to play a role in atherogenesis. IL-17 induces eotaxin secretion from smooth muscles, macrophages and fat tissue in the atheromatous plaque[39]. The recruitment of eosinophils by eotaxin during the inflammatory process was recently linked to vascular inflammation and cardiovascular disease[40]. Exploring the relation between these inflammatory mediators and oxidative modification of glycated Hb may provide new avenues for understanding the progression of atherogenic events.

In summary, accumulating evidence suggests that glycation of Hb and formation of Hb-AGE in diabetics exacerbate cellular oxidative stress releasing potent oxidants which contribute to endothelial oxidative damage and trigger a vicious cycle of oxidative/inflammatory responses. Recruitment of inflammatory mediators contributes to the progression of atherogenesis and the development of diabetic vascular complications. Designing preventive and therapeutic measures that target hemoglobin glyco-oxidative pathways may be useful tools for the management and control of atherosclerosis progression and cardiovascular disease in diabetics.

REFERENCES

1 **Stirban AO**, Tschoepe D. Cardiovascular complications in diabetes: targets and interventions. *Diabetes Care* 2008; **31** Suppl 2:

S215-S221 [PMID: 18227488 DOI: 10.2337/dc08-s257]
2 **Nwose EU**, Jelinek HF, Richards RS, Kerr PG. Erythrocyte oxidative stress in clinical management of diabetes and its cardiovascular complications. *Br J Biomed Sci* 2007; **64**: 35-43 [PMID: 17444418]
3 **Li YS**, Haga JH, Chien S. Molecular basis of the effects of shear stress on vascular endothelial cells. *J Biomech* 2005; **38**: 1949-1971 [PMID: 16084198]
4 **Watala C**, Witas H, Olszowska L, Piasecki W. The association between erythrocyte internal viscosity, protein non-enzymatic glycosylation and erythrocyte membrane dynamic properties in juvenile diabetes mellitus. *Int J Exp Pathol* 1992; **73**: 655-663 [PMID: 1329916]
5 **Piarulli F**, Sartore G, Lapolla A. Glyco-oxidation and cardiovascular complications in type 2 diabetes: a clinical update. *Acta Diabetol* 2013; **50**: 101-110 [PMID: 22763581 DOI: 10.1007/s00592-012-0412-3]
6 **John WG**, Lamb EJ. The Maillard or browning reaction in diabetes. *Eye* (Lond) 1993; **7** (Pt 2): 230-237 [PMID: 7607341]
7 **Thornalley PJ**, Rabbani N. Detection of oxidized and glycated proteins in clinical samples using mass spectrometry--a user's perspective. *Biochim Biophys Acta* 2014; **1840**: 818-829 [PMID: 23558060 DOI: 10.1016/j.bbagen.2013.03.025]
8 **Isbell H**, Frush HL. Mutarotation, Hydrolysis, and Rearrangement Reactions of Glycosylamines. *J Org Chem* 1958; **23**: 1309-1319 [DOI: 10.1021/jo01103a019]
9 **Goldin A**, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation* 2006; **114**: 597-605 [PMID: 16894049]
10 **Ott C**, Jacobs K, Haucke E, Navarrete Santos A, Grune T, Simm A. Role of advanced glycation end products in cellular signaling. *Redox Biol* 2014; **2**: 411-429 [PMID: 24624331 DOI: 10.1016/j.redox.2013.12.016]
11 **Yamagishi S**, Maeda S, Matsui T, Ueda S, Fukami K, Okuda S. Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes. *Biochim Biophys Acta* 2012; **1820**: 663-671 [PMID: 21440603 DOI: 10.1016/j.bbagen.2011.03.014]
12 **Huebschmann AG**, Regensteiner JG, Vlassara H, Reusch JE. Diabetes and advanced glycoxidation end products. *Diabetes Care* 2006; **29**: 1420-1432 [PMID: 16732039]
13 **Basta G**, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. *Cardiovasc Res* 2004; **63**: 582-592 [PMID: 15306213]
14 **American Diabetes Association.** Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]
15 **Hong LF**, Li XL, Guo YL, Luo SH, Zhu CG, Qing P, Xu RX, Wu NQ, Li JJ. Glycosylated hemoglobin A1c as a marker predicting the severity of coronary artery disease and early outcome in patients with stable angina. *Lipids Health Dis* 2014; **13**: 89 [PMID: 24884794 DOI: 10.1186/1476-511X-13-89]
16 **Cai A**, Li G, Chen J, Li X, Wei X, Li L, Zhou Y. Glycated hemoglobin level is significantly associated with the severity of coronary artery disease in non-diabetic adults. *Lipids Health Dis* 2014; **13**: 181 [PMID: 25477191 DOI: 10.1186/1476-511X-13-181]
17 **Elley CR**, Kenealy T, Robinson E, Drury PL. Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. *Diabet Med* 2008; **25**: 1295-1301 [PMID: 19046219]
18 **Turk Z**, Mesić R, Benko B. Comparison of advanced glycation endproducts on haemoglobin (Hb-AGE) and haemoglobin A1c for the assessment of diabetic control. *Clin Chim Acta* 1998; **277**: 159-170 [PMID: 9853699]
19 **Makita Z**, Vlassara H, Rayfield E, Cartwright K, Friedman E, Rodby R, Cerami A, Bucala R. Hemoglobin-AGE: a circulating marker of advanced glycosylation. *Science* 1992; **258**: 651-653 [PMID: 1411574]
20 **Sen S**, Kar M, Roy A, Chakraborti AS. Effect of nonenzymatic glycation on functional and structural properties of hemoglobin. *Biophys Chem* 2005; **113**: 289-298 [PMID: 15620514]
21 **Raghothama C**, Rao P. Degradation of glycated hemoglobin. Role of erythrocytic proteolytic enzymes and oxidant damage. *Clin Chim Acta* 1997; **264**: 13-25 [PMID: 9267699]
22 **Ortiz de Orué Lucana D**, Roscher M, Honigmann A, Schwarz J. Iron-mediated oxidation induces conformational changes within the redox-sensing protein HbpS. *J Biol Chem* 2010; **285**: 28086-28096 [PMID: 20571030 DOI: 10.1074/jbc.M110.127506]
23 **Kar M**, Chakraborti AS. Release of iron from haemoglobin--a possible source of free radicals in diabetes mellitus. *Indian J Exp Biol* 1999; **37**: 190-192 [PMID: 10641144]
24 **Shetty JK**, Prakash M, Ibrahim MS. Relationship between free iron and glycated hemoglobin in uncontrolled type 2 diabetes patients associated with complications. *Indian J Clin Biochem* 2008; **23**: 67-70 [PMID: 23105724 DOI: 10.1007/s12291-008-0016-4]
25 **Atamna H**, Ginsburg H. Heme degradation in the presence of glutathione. A proposed mechanism to account for the high levels of non-heme iron found in the membranes of hemoglobinopathic red blood cells. *J Biol Chem* 1995; **270**: 24876-24883 [PMID: 7559611]
26 **Halliwell B**. Reactive species and antioxidants. Redox biology is a fundamental theme of aerobic life. *Plant Physiol* 2006; **141**: 312-322 [PMID: 16760481 DOI: 10.1104/pp.106.077073]
27 **Jarolim P**, Lahav M, Liu SC, Palek J. Effect of hemoglobin oxidation products on the stability of red cell membrane skeletons and the associations of skeletal proteins: correlation with a release of hemin. *Blood* 1990; **76**: 2125-2131 [PMID: 2242431]
28 **Kung CM**, Tseng ZL, Wang HL. Erythrocyte fragility increases with level of glycosylated hemoglobin in type 2 diabetic patients. *Clin Hemorheol Microcirc* 2009; **43**: 345-351 [PMID: 19996523 DOI: 10.3233/CH-2009-1245]
29 **Virtue MA**, Furne JK, Nuttall FQ, Levitt MD. Relationship between GHb concentration and erythrocyte survival determined from breath carbon monoxide concentration. *Diabetes Care* 2004; **27**: 931-935 [PMID: 15047651]
30 **White CR**, Frangos JA. The shear stress of it all: the cell membrane and mechanochemical transduction. *Philos Trans R Soc Lond B Biol Sci* 2007; **362**: 1459-1467 [PMID: 17569643 DOI: 10.1098/rstb.2007.2128]
31 **Potor L**, Bányai E, Becs G, Soares MP, Balla G, Balla J, Jeney V. Atherogenesis may involve the prooxidant and proinflammatory effects of ferryl hemoglobin. *Oxid Med Cell Longev* 2013; **2013**: 676425 [PMID: 23766856 DOI: 10.1155/2013/676425]
32 **Silva G**, Jeney V, Chora A, Larsen R, Balla J, Soares MP. Oxidized hemoglobin is an endogenous proinflammatory agonist that targets vascular endothelial cells. *J Biol Chem* 2009; **284**: 29582-29595 [PMID: 19700768 DOI: 10.1074/jbc.M109.045344]
33 **Hongo K**, Ogawa H, Kassell NF, Nakagomi T, Sasaki T, Tsukahara T, Lehman RM. Comparison of intraluminal and extraluminal inhibitory effects of hemoglobin on endothelium-dependent relaxation of rabbit basilar artery. *Stroke* 1988; **19**: 1550-1555 [PMID: 3264426]
34 **Martin W**, Villani GM, Jothianandan D, Furchgott RF. Selective blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation by hemoglobin and by methylene blue in the rabbit aorta. *J Pharmacol Exp Ther* 1985; **232**: 708-716 [PMID: 2983068]
35 **Davignon J**, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation* 2004; **109**: III27-III32 [PMID: 15198963]
36 **Rodríguez-Mañas L**, Arribas S, Girón C, Villamor J, Sánchez-Ferrer CF, Marín J. Interference of glycosylated human hemoglobin with endothelium-dependent responses. *Circulation* 1993; **88**: 2111-2116 [PMID: 8106180]
37 **Singh RB**, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. *Exp Clin Cardiol* 2002; **7**: 40-53 [PMID: 19644578]
38 **Libby P**, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105**: 1135-1143 [PMID: 11877368]
39 **Tarantino G**, Costantini S, Finelli C, Capone F, Guerriero E, La Sala N, Gioia S, Castello G. Is serum Interleukin-17 associated with early atherosclerosis in obese patients? *J Transl Med* 2014; **12**: 214

[PMID: 25092442 DOI: 10.1186/s12967-014-0214-1]

40 **Falcone C**, Buzzi MP, Bozzini S, Boiocchi C, D'Angelo A, Schirinzi S, Choi J, Ochan Kilama M, Esposito C, Torreggiani M, Mancia G. Relationship between sRAGE and eotaxin-3 with CRP in hypertensive patients at high cardiovascular risk. *J Nephrol* 2013; **26**: 144-151 [PMID: 23147687 DOI: 10.5301/jn.5000122]

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REVIEW

Adipose tissue-derived stem cells as a therapeutic tool for cardiovascular disease

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Abstract

Adipose tissue-derived stem cells (ADSCs) are adult stem cells that can be easily harvested from subcutaneous adipose tissue. Many studies have demonstrated that ADSCs differentiate into vascular endothelial cells (VECs), vascular smooth muscle cells (VSMCs), and cardiomyocytes *in vitro* and *in vivo*. However, ADSCs may fuse with tissue-resident cells and obtain the corresponding characteristics of those cells. If fusion occurs, ADSCs may express markers of VECs, VSMCs, and cardiomyocytes without direct differentiation into these cell types. ADSCs also produce a variety of paracrine factors such as vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor-1 that have proangiogenic and/or antiapoptotic activities. Thus, ADSCs have the potential to regenerate the cardiovascular system *via* direct differentiation into VECs, VSMCs, and cardiomyocytes, fusion with tissue-resident cells, and the production of paracrine factors. Numerous animal studies have demonstrated the efficacy of ADSC implantation in the treatment of acute myocardial infarction (AMI), ischemic cardiomyopathy (ICM), dilated cardiomyopathy, hindlimb ischemia, and stroke. Clinical studies regarding the use of autologous ADSCs for treating patients with AMI and ICM have recently been initiated. ADSC implantation has been reported as safe and effective so far. Therefore, ADSCs appear to be useful for the treatment of cardiovascular disease. However, the tumorigenic potential of ADSCs requires careful evaluation before their safe clinical application.

Key words: Adipose tissue-derived stem cells; Cardiovascular disease; Acute myocardial infarction; Ischemic cardiomyopathy; Hindlimb ischemia; Stroke

Core tip: Adipose tissue-derived stem cells (ADSCs) have been used for the treatment of cardiovascular disease with the efficacy of ADSC implantation demonstrated in animal models. However, the mechanisms under-

lying the capacity of ADSCs for regenerating the cardiovascular system remain controversial. ADSCs may differentiate into blood vessels and cardiomyocytes, fuse with other cell types, obtaining the characteristics of those cells, and secrete paracrine factors that have proangiogenic and/or antiapoptotic activities. This review also discusses recently initiated clinical trials using autologous ADSCs.

Suzuki E, Fujita D, Takahashi M, Oba S, Nishimatsu H. Adipose tissue-derived stem cells as a therapeutic tool for cardiovascular disease. *World J Cardiol* 2015; 7(8): 454-465 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i8/454.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i8.454

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Despite advances in the treatment of acute myocardial infarction (AMI) using percutaneous coronary intervention, the treatment of heart failure (HF), which occurs as a result of the death of myocardial tissues and subsequent tissue remodeling, is still a challenging problem. As cardiomyocytes are terminally differentiated cells with minimal regenerative capacity, heart transplantation is currently the only treatment option for end-stage ischemic heart disease. The development of new therapies for AMI and HF is required to meet this substantial clinical requirement. Thus, stem cell therapy for CVD has recently gained substantial attention.

Stem cells are defined as cells capable of self-renewal and differentiation into a variety of phenotypes[1]. Stem cells comprise embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs were originally isolated from the inner cell mass of blastocysts[2], and are pluripotent stem cells capable of giving rise to all three germ layers. However, several issues, including ethical concerns and teratoma formation, limit the clinical use of ESCs. Induced pluripotent stem (iPS) cells are also pluripotent stem cells that have very similar characteristics to ESCs[3,4]. As ethical problems can be avoided, iPS cells represent a potentially promising option for stem cell therapy. However, cancer formation is a major issue that needs to be overcome before widespread acceptance of the use of iPS cells in clinical settings. ASCs are multipotent stem cells that reside in various adult tissues. Among ASCs, bone marrow-derived mesenchymal stem cells (BMMSCs) and adipose tissue-derived stem cells (ADSCs) are the most extensively studied. BMMSCs are reported to have the potential to differentiate into various cell types including bone, cartilage, cardiac muscle, skeletal muscle, vascular endothelial cells (VECs), and vascular smooth muscle cells (VSMCs)[5,6]. BMMSCs have been used to treat CVD in clinical settings, with promising results reported in a number of studies[7-14], although other studies failed to demonstrate positive outcomes[15,16]. ADSCs have gained substantial attention recently as subcutaneous adipose tissues are abundant and can be easily harvested using liposuction, a procedure that is less invasive than bone marrow aspiration, with minimal donor discomfort. Adipose tissue contains a significantly greater proportion of stem cells than the bone marrow (5% *vs* 0.01%) and is therefore a convenient source of stem cells[17]. Furthermore, ADSCs reportedly do not express class II major histocompatibility complexes[18,19], suggesting that ADSCs may be suitable for allogenic transplantation in addition to autologous transplantation. In this review, we discuss the characteristics of ADSCs and their potential use in the treatment of CVD.

CLASSIFICATION OF ADSCS

ADSCs can be obtained from subcutaneous adipose tissues with the use of collagenase digestion. Freshly isolated ADSCs (fADSCs) are known to be heterogeneous and contain hematopoietic cells ($CD45^+$ and/or $CD34^+$) and VECs ($CD34^+/CD31^+$) in addition to stem cells ($CD44^+$ and $CD105^+$)[20]. fADSCs can be cultured on plastic dishes in the presence of fetal bovine serum (FBS). Non-adherent cells, those that do not attach to plastic dishes, can be removed to obtain cultured ADSCs (cADSCs), a relatively homogeneous population that expresses stem cell markers, such as CD44 and CD105, but not hematopoietic lineage markers, including CD11b, CD45, and CD34 or the VEC marker CD31[21,22]. Artificially-modified ADSCs (mADSCs) are a type of ADSCs produced through the introduction of specific genes[23,24] or pre-treatment with drugs[25] before administration. The purpose of artificial modification is to improve the function of ADSCs, such as proangiogenic and antiapoptotic activities. cADSCs have been the most widely used type, particularly in animal studies. However, fADSCs may be more suitable for clinical applications for several reasons. First, fADSCs can be rapidly prepared compared with cADSCs as cell culture is not required while preparing fADSCs. The rapid preparation and administration of stem cells may be required to achieve sufficient recovery from tissue ischemia when treating AMI or critical hindlimb ischemia. Second, the preparation of fADSCs is technically less challenging compared with that of cADSCs as it does not require the use of foreign materials such as FBS. ADSCs used in clinical settings must not contain any foreign materials derived from animals or humans other than the individual patient receiving the stem cell therapy. Therefore, it is desirable to avoid culturing in the preparation of ADSCs for clinical applications.

DIFFERENTIATION POTENTIAL OF ADSCS *IN VITRO*

ADSCs have the potential to differentiate into cartilage,

Table 1 Differentiation potential of adipose tissue-derived stem cells *in vitro*

Cell type	Expression of VEC markers	Expression of VSMC markers	Expression of cardiomyocyte markers	Production of paracrine factors	Ref.
Human fADSCs	CD31, vWF	NE	NE	NE	Miranville *et al*[30]
Human cADSCs	CD31, vWF	NE	NE	NE	Planat-Benard *et al*[31]
Human cADSCs	NE	SMA, calponin, caldesmon, myosin heavy chain, SM22α	NE	NE	Rodríguez *et al*[32]
Human cADSCs	NE	SMA, calponin, SM22α	NE	NE	Jeon *et al*[33]
Rabbit cADSCs	NE	NE	Myosin heavy chain, sarcomeric α-actinin, troponin I	NE	Rangappa *et al*[34]
Human cADSCs	NE	NE	Sarcomeric α-actinin, desmin, cardiac troponin	NE	Gaustad *et al*[35]
Murine fADSCs	NE	NE	GATA-4, Nkx2.5	NE	Planat-Bénard *et al*[36]
Human cADSCs	NE	NE	NE	VEGF, HGF, TGF-β	Rehman *et al*[44]
Murine cADSCs	ND	ND	NE	VEGF, HGF	Nakagami *et al*[45]
Human cADSCs	NE	NE	NE	VEGF, IGF-1	Sadat *et al*[46]

NE: Not examined; ND: Not detected; ADSCs: Adipose tissue-derived stem cells; VEC: Vascular endothelial cell; TGF: Transforming growth factor; VSMC: Vascular smooth muscle cell; HGF: Hepatocyte growth factor; IGF-1: Insulin-like growth factor-1; vWF: von Willebrand factor.

bone, tendon, and fat when cultured under lineage-specific conditions[26-29]. Furthermore, ADSCs have the potential to differentiate into VECs, VSMCs, and cardiomyocytes *in vitro* (Table 1), the main components of the cardiovascular system. Miranville *et al*[30] isolated and examined the characteristics of human fADSCs. Human fADSCs were found to express CD34 (27.6%-63.4%) with CD34 positive cells shown to be composed of two populations: $CD34^+/CD31^+$ cells (probably VECs) and $CD34^+/CD31^-$ cells. The authors demonstrated $CD34^+/CD31^-$ cells expressed CD31 and von Willebrand factor (vWF) when cultured in a medium containing vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF). Planat-Benard *et al*[31] used relatively fresh human cADSCs cultured on plastic dishes for 3 d without passaging. Approximately 90% of these cells were found to express CD34, and they expressed VEC markers, including CD31 and vWF, when cultured in a semisolid medium. Rodríguez *et al*[32] studied human cADSCs cultured in MCDB 131 medium supplemented with 1% FBS. The authors found these cells expressed VSMC markers, including α-smooth muscle actin (SMA), calponin, caldesmon, myosin heavy chain, and smooth muscle protein 22-α (SM22α). Furthermore, differentiated cells contracted in response to carbachol demonstrated contractile capacity. Jeon *et al*[33] demonstrated the use of sphingosylphosphorylcholine (SPC) to induce the differentiation of human cADSCs into VSMCs, as determined by SMA, calponin, and SM22α expression. They also found that SPC-induced differentiation of ADSCs into VSMCs depended on transforming growth factor-β (TGF-β), shown to be secreted by ADSCs in an autocrine manner. Rangappa *et al*[34] incubated rabbit cADSCs with 5-azacytidine. The authors demonstrated that these cells differentiated into spontaneously beating cardiomyocytes with expression of myosin heavy chain, sarcomeric α-actinin, and troponin I. Gaustad *et al*[35] incubated human cADSCs with rat cardiomyocyte extracts and demonstrated ADSC expression of cardiomyocyte markers, including sarcomeric α-actinin, desmin, and cardiac troponin I. Differentiated cells were also shown to beat autonomously. Planat-Bénard *et al*[36] cultured murine fADSCs in a semisolid methylcellulose medium without 5-azacytidine and found that ADSCs expressed cardiac-specific markers, such as transcription factors, GATA-4, and Nkx2.5. These cells demonstrated spontaneous beating with acceleration in response to isoproterenol, a β-agonist, and deceleration in response to carbamylcholine, an acetylcholine agonist.

DIFFERENTIATION POTENTIAL OF ADSCS *IN VIVO*

It has also been suggested that ADSCs express VEC, VSMC, and cardiomyocyte markers *in vivo* (Table 2). For example, cADSCs administered in a hindlimb ischemia model[31] and AMI model[37] were reportedly incorporated into tissues and were found to express VEC markers, such as CD31 and vWF. ADSC implantation has been shown to improve blood flow in a murine hindlimb ischemia model[31]. Jack *et al*[38] injected human cADSCs into the bladder and urethra and demonstrated the expression of SMA, a marker for VSMCs, by engrafted cells. Valina *et al*[37] injected porcine cADSCs into the coronary artery following the induction of AMI and found that a proportion of engrafted cells expressed SMA. The authors also found that left ventricular function recovered following administration of ADSCs. Strem *et al*[39] prepared fADSCs from Rosa 26 mice ubiquitously expressing β-galactosidase and injected these cells into the intraventricular chamber following myocardial cryoinjury. The authors demonstrated co-expression of β-galactosidase with myosin heavy chain, Nkx2.5, and troponin I. Yamada *et al*[40] transplanted the CD29 positive fraction of murine cADSCs into the infarct border zone of an AMI model and demonstrated

Table 2 Differentiation potential of adipose tissue-derived stem cells *in vivo*

Cell type	Animal model	Expression of VEC markers	Expression of VSMC markers	Expression of cardiomyocyte markers	Functional recovery	Ref.
Human cADSCs	Murine hindlimb ischemia	CD31	NE	NE	Yes	Planat-Benard *et al*[31]
Porcine cADSCs	Porcine AMI	vWF	SMA	NE	Yes	Valina *et al*[37]
Human cADSCs	Bladders and urethras of athymic rats and SCID mice	NE	SMA	NE	NE	Jack *et al*[38]
Murine fADSCs	Murine AMI	NE	NE	Myosin heavy chain, Nkx2.5, troponin I	Yes	Strem *et al*[39]
Murine fADSCs	Rat AMI	NE	NE	Sarcomeric actin, GATA-4	Yes	Yamada *et al*[40]
Conditioned medium from human cADSCs	Murine hindlimb ischemia	NE	NE	NE	Yes	Bhang *et al*[48]

NE: Not examined; VSMC: Vascular smooth muscle cell; ADSCs: Adipose tissue-derived stem cells; vWF: von Willebrand factor; VEC: Vascular endothelial cell; SMA: Smooth muscle actin; AMI: Acute myocardial infarction.

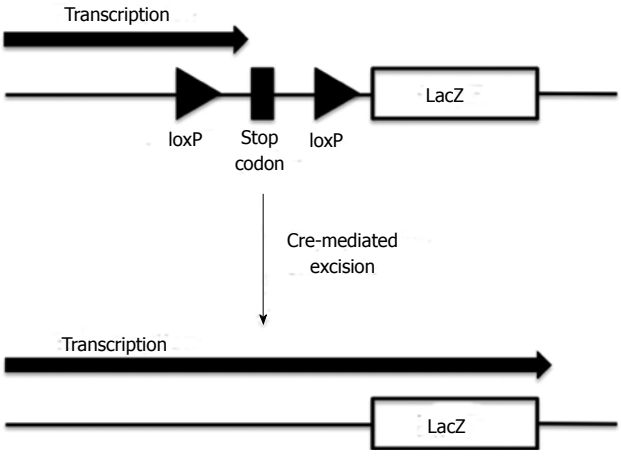

Figure 1 Schematic representation of LacZ expression following the excision of a floxed stop codon by Cre recombinase.

the expression of cardiomyocyte markers, such as sarcomeric actin and GATA-4. Furthermore, improved left ventricular function was observed in this study.

However, cell fusion should be considered carefully before concluding that ADSCs have the potential to differentiate into VECs, VSMCs, or cardiomyocytes *in vivo*. The *in vivo* fusion of administered ADSCs with tissue-resident VECs, VSMCs, and/or cardiomyocytes may lead to ADSCs acquiring the phenotypes of the corresponding fused cell types, making it appear as if ADSCs are directly differentiating into these cell types. In fact, cell fusion has been shown to occur with the *in vivo* administration of BMMSCs. Alvarez-Dolado *et al*[41] used R26R mice that contain a *lacZ* reporter gene downstream of a stop codon flanked by loxP sites (floxed). The *lacZ* reporter gene was therefore only expressed when the loxP-flanked stop codon was excised by Cre recombinase (Figure 1). The authors lethally irradiated these mice and transplanted BMMSCs from mice that ubiquitously express Cre recombinase and green fluorescent protein (GFP). If cells from the donor and recipient fused, the Cre enzyme would excise the Lox P-flanked stop codon, thereby allowing the expression of the *lacZ* gene. The results of this study revealed β-gal$^+$ (fused) and GFP$^+$ cells in the brain, heart, and liver of recipients, at 2 and 4 mo post-transplantation. Thus, BMMSCs potentially fuse with other cell types *in vivo*. There have been no reports so far clearly demonstrating the fusion of ADSCs with other cell types *in vivo*. Bai *et al*[42] injected both human fADSCs and cADSCs into murine hearts and examined the occurrence of cell fusion using fluorescence *in situ* hybridization to detect human X chromosomes and murine Y chromosomes. The authors did not detect co-localization of human X chromosomes with murine Y chromosomes in individual cells, excluding the possibility of cell fusion events. However, similar techniques used to detect cell fusion by BMMSCs (*e.g.*, the transplantation of ADSCs derived from transgenic mice expressing Cre recombinase into recipients expressing a *lacZ* reporter gene downstream of a floxed stop codon) should be used to conclusively determine whether ADSCs fuse with other tissue-resident cell types. Interestingly, Metzele *et al*[43] artificially fused human cADSCs with neonatal rat cardiomyocytes using hemagglutinating virus of Japan. The authors demonstrated spontaneous beating of fused ADSCs and the expression of human troponin I, suggesting fused ADSCs produced cardiomyogenic proteins. Furthermore, fused ADSCs were positive for the cell proliferation marker Ki67, suggesting proliferating capacity in marked contrast to terminally differentiated cardiomyocytes that are unable to proliferate. Therefore, ADSCs may stimulate the regeneration of heart muscles through *in vivo* fusion with cardiomyocytes.

PRODUCTION OF PARACRINE FACTORS BY ADSCS

ADSCs have been shown to produce a variety of proangiogenic and antiapoptotic factors. Rehman *et al*[44] examined the production of paracrine factors by human cADSCs. The authors showed that ADSCs produced VEGF, hepatocyte growth factor (HGF), and TGF-β. VEGF production increased five-fold when ADSCs were cultured under hypoxic conditions. Condi-

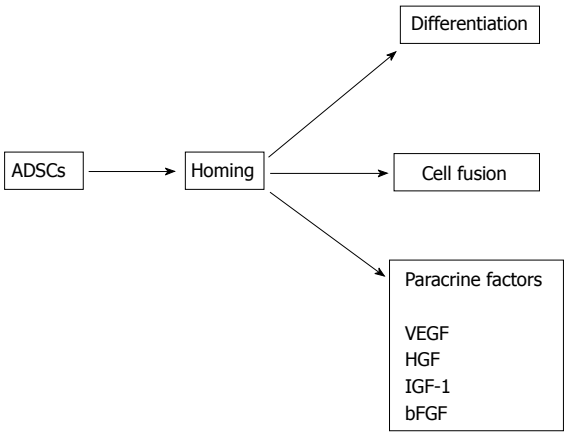

Figure 2 Possible mechanisms underlying the effect of adipose tissue-derived stem cells on regeneration of the cardiovascular system. ADSCs: Adipose tissue-derived stem cells; VEGF: Vascular endothelial growth factor; HGF: Hepatocyte growth factor; IGF-1: Insulin-like growth factor-1; bFGF: Basic fibroblast growth factor.

tioned medium (CM) obtained from hypoxic ADSCs significantly increased the proliferation and survival of VECs. Furthermore, the administration of these ADSCs significantly improved perfusion in a hindlimb ischemia model. Nakagami *et al*[45] reported murine cADSCs produce VEGF and HGF. The authors also administered ADSCs in a mouse hindlimb ischemia model and found transplanted ADSCs improved blood flow. However, transplanted ADSCs did not express VEC or VSMC markers, suggesting that ADSCs did not differentiate into vascular components in this study. Sadat *et al*[46] demonstrated human cADSCs produce VEGF and IGF-I and that these cytokines contribute to the antiapoptotic effects of ADSCs on cardiomyocytes. The authors implicated the secretion of VEGF by ADSCs in the ADSC-induced stimulation of tube formation by VECs. Yeghiazarians *et al*[47] administered BMMSCs and their lysates into the heart in a murine AMI model. The authors revealed that both BMMSCs and their lysates improved cardiac function and histology to similar extents, suggesting cytokines produced by BMMSCs, but not cells *per se*, are required for the recovery of cardiac function. Bhang *et al*[48] used a three-dimensional spheroid culture of human ADSCs to prepared CM. The authors injected CM into ischemic regions in a murine hindlimb ischemia model. They detected restoration of blood perfusion in this model. Albersen *et al*[49] injected rat cADSCs and their lysates into the penis in a rat model of cavernous nerve injury. The authors found that both ADSCs and their lysates restored erectile function to similar extents. These results suggest substances secreted by ADSCs, rather than cells *per se*, are critical for their regenerative function. Collectively, these results suggest that paracrine factors produced by ADSCs play a major, if not all, role in the regeneration of the cardiovascular system, although the differentiation and cell fusion of ADSCs may also be involved. The possible mechanisms underlying the regenerative effects of ADSCs on the cardiovascular system are summarized in Figure 2.

SURVIVAL OF ADSCS *IN VIVO*

The survival and engraftment of ADSCs *in vivo* have been examined within 30 d of ADSC implantation in the majority of studies[37,50-53]. Yin *et al*[54] injected swine cADSCs into the coronary artery following induction of AMI and examined the fate of ADSCs 8 wk after injection. The authors found that many ADSCs expressed troponin T and α-sarcomeric actin, indicating the ability of ADSCs to survive for 8 wk. Bai *et al*[42] introduced a luciferase reporter gene into human cADSCs and transplanted these cells into the murine heart muscle using an AMI model. The authors detected luciferase-positive ADSCs by bioluminescence imaging. Bioluminescence was observed 16 wk after ADSC transplantation, indicating that some ADSCs survived for 16 wk. However, murine cADSCs transplanted in a hindlimb ischemia model were found to barely remain in ischemic tissues 28 d after transplantation[45]. Therefore, the survival and engraftment of ADSCs in recipient tissues appear to vary according to the animal species and experimental models used.

APPLICATION OF ADSCS TO TREAT CVD

AMI and ischemic cardiomyopathy

Many studies have demonstrated the efficacy of ADSC administration in recovering cardiac function in AMI models. cADSCs have been predominantly used in animal models[37,39,40,51-57], although fADSCs[58] and mADSCs[23-25,59] have also been used. ADSCs have been transplanted *via* the coronary artery[37,53,54,57] and directly into cardiac muscles[23-25,39,40,51,55,56,58,59] in previous studies. Although ADSC implantation into the heart showed efficacy in recovering cardiac function in most studies, the underlying mechanisms remain controversial. Transplanted ADSCs expressed VEC, VSMC, or cardiomyocyte markers in numerous studies[37,39,40,52-55,57,59]; however, the "differentiation" of ADSCs was either not detected or examined in other studies[23-25,51,56,58]. Bai *et al*[42] transplanted both fADSCs and cADSCs in a murine AMI model and found both cell types recovered cardiac function to a similar extent. A proportion of transplanted fADSCs and cADSCs were found to express cardiomyocyte markers, including troponin I and connexin 43. These results are encouraging as fADSCs may be more suitable for clinical applications than cADSCs for reasons outlined above. ADSCs differentiated into specific cell types have been used to treat chronic MI. Okura *et al*[60] induced the differentiation of human cADSCs into cardiomyoblast-like cells (CLCs) *in vitro* and transplanted these cells into the swine coronary arteries 4 wk following the induction of MI. Cardiac function was

recovered by CLC implantation. Furthermore, implanted CLCs expressed human α-cardiac actin, Nkx2.5, and GATA-4. Several studies have used a monolayer sheet to transplant ADSCs into chronic MI models. Miyahara *et al*[61] cultured rat ADSCs on a temperature-responsive polymer to prepare a monolayer of ADSCs. The authors transplanted these cells onto scarred myocardium at 4 wk following coronary ligation. Transplanted cells grew *in situ* to form a thick stratum containing newly-formed blood vessels. The transplantation of monolayered cells prevented ventricular wall scarring and improved cardiac function. Okura *et al*[62] induced the differentiation of human cADSCs into CLCs *in vitro* and prepared monolayer sheets of human CLCs and ADSCs using a temperature-responsive polymer. The authors then transplanted these cells onto the infarcted areas of rats 4 wk following the induction of MI. The authors demonstrated that the implantation of CLCs, but not ADSCs, resulted in a long-term recovery of cardiac function and improved survival. Furthermore, CLCs, but not ADSCs, were found to express human troponin I.

Clinical trials of ADSCs in the treatment of AMI have recently been initiated. The AdiPOse-derived stem ceLLs in the treatment of patients with ST-elevation myOcardial infarction (APOLLO) trial is a double-blind, placebo-controlled, phase Ⅰ/Ⅱa trial[63]. Autologous fADSCs were transplanted into the coronary artery of AMI patients with ST-segment elevation following successful revascularization. During the 6-mo follow-up period, improvements in the left ventricular ejection fraction and myocardial perfusion and reductions in the infarct size were demonstrated. The subsequent phase Ⅱ/Ⅲ trial, called ADVANCE, is currently ongoing. In this trial, AMI patients with ST elevation are treated with intracoronary implantation of autologous fADSCs. The primary endpoint is reduction in the infarct size as measured by magnetic resonance imaging. The adiPose-deRived stEm Cells In the treatment of patients with non revaScularizable ischEmic myocardium (PRECISE) trial enrolled patients who had chronic ischemic cardiomyopathy (ICM) not amenable to any revascularization procedures[64]. Autologous fADSCs were transplanted into cardiac muscles from endocardial sites. Maximal oxygen consumption and total left ventricular mass were significantly improved by ADSCs implantation. The ATHENA trial is an ongoing clinical trial intending to treat patients who have chronic ICM with HF symptoms using autologous fADSCs. The endpoints of this trial include peak oxygen consumption, perfusion defects, HF symptoms, left ventricle end-systolic and diastolic volume, and ejection fraction.

Dilated cardiomyopathy

Several studies have demonstrated the efficacy of ADSC implantation in the recovery of cardiac function using dilated cardiomyopathy (DCM) models. Lin *et al*[65] used a rat DCM model induced by the injection of porcine myosin and implanted cADSCs into cardiac muscle. The effect of combination therapy with ADSCs and sildenafil, a phosphodiesterase type-5 inhibitor, was also evaluated. This study found that either ADSCs implantation alone or sildenafil treatment alone was effective for the recovery of cardiac function, with combination therapy being the most effective. Hamdi *et al*[66] transplanted a monolayer sheet of murine cADSCs onto the heart surface in a murine DCM model, in which a floxed serum response factor gene is conditionally deleted using the expression of Cre recombinase. The authors found many blood vessels in transplanted sheets and some transplanted ADSCs in the cardiac muscle, a proportion of which expressed CD31. The authors further demonstrated the recovery of cardiac function and significant reduction of cardiac fibrosis following ADSC transplantation. Pınarlı *et al*[67] transplanted cADSCs into a doxorubicin-induced HF model. They further examined combination therapy of ADSC transplantation with resveratrol, a polyphenolic compound found in red grapes with an antioxidant activity. This study found either ADSC implantation alone, or resveratrol administration alone, was effective in recovering cardiac function, although combination therapy was found to be most effective.

Hindlimb ischemia

A number of studies have demonstrated that ADSC implantation improves blood flow in animal hindlimb ischemia models. fADSCs[30,68], cADSCs[31,45,48,69-76], and mADSCs[77] have all been used in these studies. Although the efficacy of ADSC administration in the recovery of blood flow appears conclusive, the mechanisms underlying the ability of ADSCs to recover blood flow remain controversial. ADSCs have been shown to engraft and express VEC and/or VSMC markers in some studies[30,31,69,70,72,75,77]. However, other studies have shown that engraftment was either not observed or examined[68,76] or paracrine factors secreted by ADSCs appeared to predominantly mediate the recovery of blood flow[45,48,70,71,73,74,77]. Lee *et al*[76] performed the transplantation of autologous cADSCs in 15 patients with critical limb ischemia. Although this was a pilot study, ADSC implantation caused no complications during the follow-up period and clinical improvement was observed in 66.7% patients. Larger-scale clinical studies are required to conclusively evaluate the efficacy and safety of ADSC transplantation in the treatment of limb ischemia.

Stroke

Several studies have demonstrated ADSC implantation induces functional recovery following brain ischemia in animal models of cerebral infarction (CI)[78-81]. Kang *et al*[78] occluded the middle cerebral artery (MCA) to induce CI and transplanted human cADSCs into the lateral ventricle. Transplanted ADSCs migrated to the border zone of the injured area and intact brain tissue and into injured areas. A proportion of ADSCs were found to express microtubule-associated protein 2 (MAP2), a neuron marker, and glial fibrillary acid

protein (GFAP), an astrocyte marker. Furthermore, ADSC implantation improved motor and somatosensory behavior following CI, although no reduction in the area of CI was observed following ADSC implantation. Gutiérrez-Fernández *et al*[79] injected cADSCs intravenously following MCA occlusion in rats and found a significant recovery of motor function, although no reduction in the infarct size or ADSC engraftment into damaged tissues was observed. Furthermore, the expression of VEGF, synaptophysin, a neuron marker, and neurofilament was significantly increased following ADSC injection, although it was not examined whether ADSCs *per se* produced these molecules. Liu *et al*[80] transplanted human cADSCs into the right corpus striatum and cerebral cortex of rats following MCA occlusion. Neurological deficits were significantly attenuated by ADSC administration. Significantly increased expression of brain-derived neurotrophic factor (BDNF), nerve growth factor, and basic fibroblast growth factor mRNA and increased protein levels of BDNF and Bcl-2 were observed following ADSC transplantation, although it was not examined whether ADSCs produced these molecules.

Coronary artery restenosis

Balloon injury of the carotid artery and wire injury of the femoral artery have been widely used as models of coronary artery restenosis. We implanted rat cADSCs around the femoral artery from the adventitial side following wire injury of the femoral artery and found that ADSC implantation significantly inhibited neointimal formation and stimulated re-endothelialization[82]. We also demonstrated that ADSCs produced angiopoietin-1 (Ang-1) and that the effect of ADSC administration diminished when expression of Ang-1 was suppressed using small interfering RNA (siRNA) against Ang-1[83] (Figure 3), indicating that Ang-1 produced by ADSCs plays a critical role in the inhibition of neointimal formation. Although drug-eluting stents (DES) are widely used and they potently inhibit restenosis, the use of DES does not always improve patient outcomes, most likely due to increased risk of late thrombosis[84,85]. Because DES inhibit the proliferation of VECs as well as VSMCs by secreting antiproliferative drugs, DES may delay re-endothelialization, resulting in thrombus formation. Therefore, agents that stimulate re-endothelialization, such as Ang-1, may be more suitable for the suppression of neointimal formation than currently used inhibitors of cell proliferation. Systematic analysis of ADSC cytokine production is required to identify molecules that inhibit neointimal formation and stimulate re-endothelialization.

FUTURE DIRECTIONS

Careful examination of the following points is required before the safe and effective clinical application of ADSCs.

Tumorigenesis

Although ADSCs may be less prone to forming tumors than ESCs, it has been reported that BMMSCs form tumors *in vivo*[86]. Furthermore, several reports have suggested ADSCs promote the proliferation of cancer cells both *in vitro* and *in vivo*[87-89]. Therefore, ADSCs may stimulate the growth of pre-existing tumors even if ADSCs *per se* do not form tumors.

Effects of age and comorbid diseases on the function of ADSCs

Patients suffering from CVD are often older and have comorbid diseases, such as hypertension and diabetes. When considering the autologous transplantation of ADSCs in these patients, it is necessary to examine whether age and comorbid diseases affect the function of ADSCs. Several studies have demonstrated that ADSCs collected from aged patients have less capacity for proliferation and differentiation compared to those collected from young donors[90-92]. Furthermore, several reports have shown that ADSCs collected from diabetic mice, hemodialysis patients, and HF patients have less capacity for proliferation, differentiation, or proangiogenic cytokine production[93-95]. Therefore, patients requiring ADSC transplantation for the treatment of CVD may not have access to high-quality autologous ADSCs. Allogenic transplantation of ADSCs may be required in these patients.

Improved ADSC survival and function

The use of mADSCs may improve the survival and/or function of ADSCs. The incubation of ADSCs with chemical compounds, culture in hypoxic conditions, or the introduction of ectopic genes are all potential methods for the pre-implantation modification of ADSCs. It is noteworthy that ADSCs cultured under hypoxic conditions have demonstrated increased capacity for proliferation, proangiogenic cytokine production, and maintenance of stemness[96-98]. The incubation of fADSCs under hypoxic conditions prior to implantation into patients may be a feasible strategy for improving the results of ADSC implantation.

Identification of paracrine factors

ADSCs produce a variety of paracrine factors, as aforementioned, and these factors appear to play a major role in the regeneration of the cardiovascular system. Elucidation of cytokine combinations with the greatest efficacy in the regeneration of the cardiovascular system may remove the need for ADSC implantation in the future.

CONCLUSION

Evidence accumulated from animal studies has indicated that ADSCs show efficacy in the treatment of CVD including AMI, ICM, and critical limb ischemia. Clinical trials have reported the safety and efficacy of ADSC

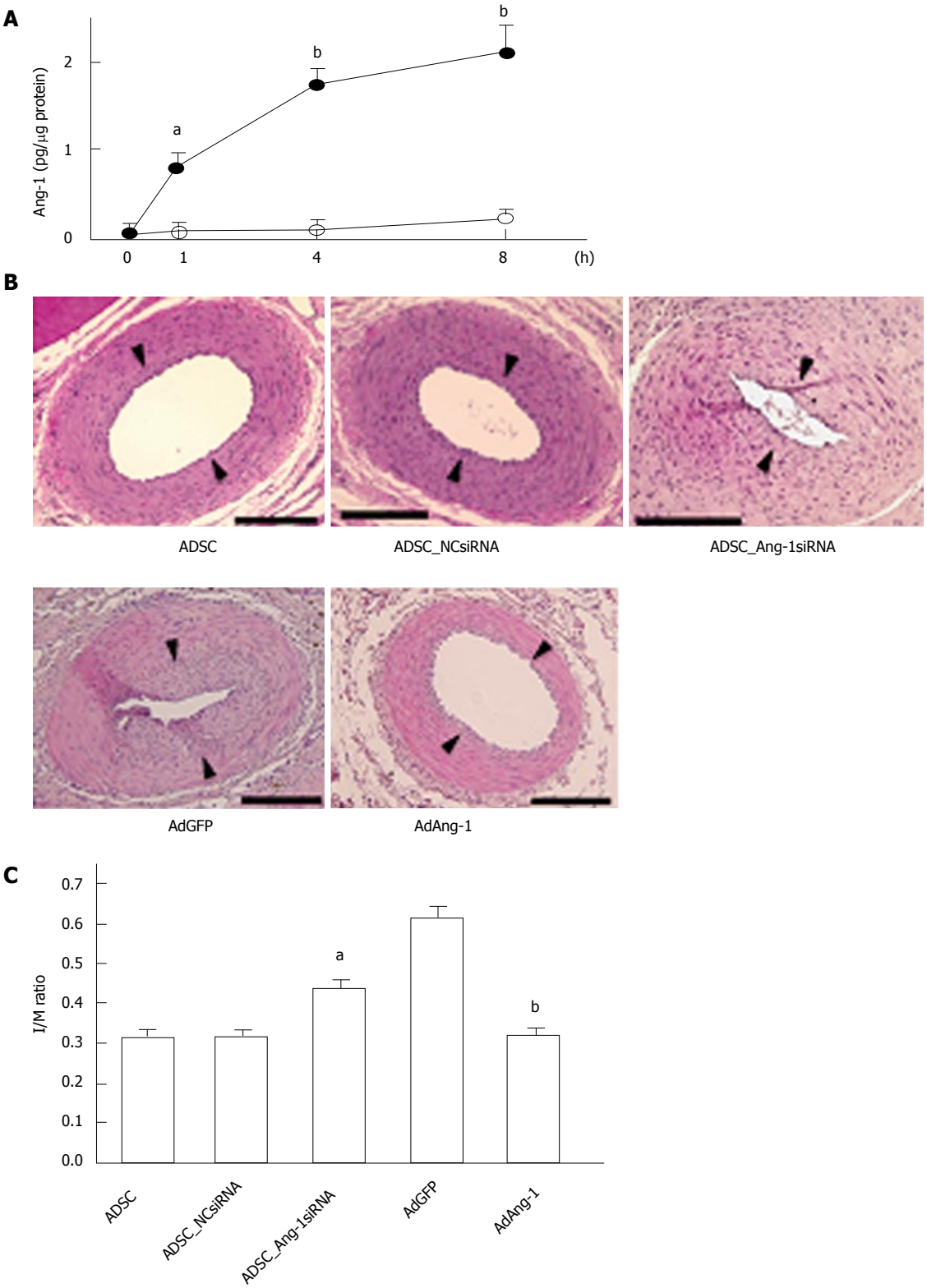

Figure 3 Ang-1 is implicated in Adipose tissue-derived stem cell-induced suppression of neointimal formation. A: ADSCs produce Ang-1, particularly when cultured in medium containing growth factors for VECs. Rat ADSCs were plated in 24-well plates and cultured in control medium (open circles) or medium containing growth factors for VECs (EGM: closed circles) for 1 wk. After washing with PBS, the medium was replaced with serum-free Dulbecco's modified Eagle medium and incubated for the indicated periods. Ang-1 accumulation was measured with an enzyme-linked immunosorbent assay kit. $^{a}P < 0.05$, $^{b}P < 0.01$ *vs* 0 h ($n = 6$ per group); B: Effect of knockdown of endogenous Ang-1 in ADSCs and forced expression of Ang-1 on neointimal formation. ADSCs were infected with lentivirus expressing negative control siRNA (NCsiRNA), which does not suppress the expression of mammalian mRNA, or lentivirus expressing Ang-1 siRNA (Ang-1siRNA). ADSCs not infected with lentivirus were used as positive controls (ADSC). ADSCs were cultured in EGM for 1 wk. ADSCs (10^6 cells) were seeded from the adventitial side immediately after wire injury of the rat femoral artery. Adenoviruses expressing green fluorescent protein (AdGFP) or Ang-1 (AdAng-1) were also injected into the femoral artery from the adventitial side following wire injury. Femoral arteries were harvested 14 d after injury for histological analyses. Arrowheads indicate the position of internal elastic lamina. Bars represent 100 μm; C: I/M ratios were compared among the groups ($n = 8$ per group). $^{a}P < 0.05$ *vs* NCsiRNA infection and $^{b}P < 0.01$ *vs* AdGFP infection. PBS: Phosphate-buffered saline; ADSCs: Adipose tissue-derived stem cells; VECs: Vascular endothelial cells.

implantation in the treatment of CVD. ADSCs may regenerate tissues through a number of mechanisms including direct differentiation into VECs, VSMCs, and cardiomyocytes, fusion with tissue-resident cells, and secretion of proangiogenic and antiapoptotic cytokines. The malignant potential of ADSCs should be carefully examined in the future.

REFERENCES

1 **Morrison SJ**, Shah NM, Anderson DJ. Regulatory mechanisms in stem cell biology. *Cell* 1997; **88**: 287-298 [PMID: 9039255 DOI: 10.1016/S0092-8674(00)81867-X]

2 **Evans MJ**, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. *Nature* 1981; **292**: 154-156 [PMID: 7242681 DOI: 10.1038/292154a0]

3 **Takahashi K**, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; **126**: 663-676 [PMID: 16904174 DOI: 10.1016/j.cell.2006.07.024]

4 **Takahashi K**, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; **131**: 861-872 [PMID: 18035408 DOI: 10.1016/j.cell.2007.11.019]

5 **Herzog EL**, Chai L, Krause DS. Plasticity of marrow-derived stem cells. *Blood* 2003; **102**: 3483-3493 [PMID: 12893756 DOI: 10.1182/blood-2003-05-1664]

6 **Grove JE**, Bruscia E, Krause DS. Plasticity of bone marrow-derived stem cells. *Stem Cells* 2004; **22**: 487-500 [PMID: 15277695 DOI: 10.1634/stemcells.22-4-487]

7 **Tateishi-Yuyama E**, Matsubara H, Murohara T, Ikeda U, Shintani S, Masaki H, Amano K, Kishimoto Y, Yoshimoto K, Akashi H, Shimada K, Iwasaka T, Imaizumi T. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet* 2002; **360**: 427-435 [PMID: 12241713 DOI: 10.1016/S0140-6736(02)09670-8]

8 **Abdel-Latif A**, Bolli R, Tleyjeh IM, Montori VM, Perin EC, Hornung CA, Zuba-Surma EK, Al-Mallah M, Dawn B. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med* 2007; **167**: 989-997 [PMID: 17533201 DOI: 10.1001/archinte.167.10.989]

9 **Assmus B**, Rolf A, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Tillmanns H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Tonn T, Dimmeler S, Dill T, Zeiher AM, Schächinger V. Clinical outcome 2 years after intracoronary administration of bone marrow-derived progenitor cells in acute myocardial infarction. *Circ Heart Fail* 2010; **3**: 89-96 [PMID: 19996415 DOI: 10.1161/CIRCHEARTFAILURE.108.843243]

10 **Leistner DM**, Fischer-Rasokat U, Honold J, Seeger FH, Schächinger V, Lehmann R, Martin H, Burck I, Urbich C, Dimmeler S, Zeiher AM, Assmus B. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI): final 5-year results suggest long-term safety and efficacy. *Clin Res Cardiol* 2011; **100**: 925-934 [PMID: 21633921 DOI: 10.1007/s00392-011-0327-y]

11 **Walter DH**, Krankenberg H, Balzer JO, Kalka C, Baumgartner I, Schlüter M, Tonn T, Seeger F, Dimmeler S, Lindhoff-Last E, Zeiher AM. Intraarterial administration of bone marrow mononuclear cells in patients with critical limb ischemia: a randomized-start, placebo-controlled pilot trial (PROVASA). *Circ Cardiovasc Interv* 2011; **4**: 26-37 [PMID: 21205939 DOI: 10.1161/CIRCINTERVENTIONS.110.958348]

12 **Williams AR**, Trachtenberg B, Velazquez DL, McNiece I, Altman P, Rouy D, Mendizabal AM, Pattany PM, Lopera GA, Fishman J, Zambrano JP, Heldman AW, Hare JM. Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling. *Circ Res* 2011; **108**: 792-796 [PMID: 21415390 DOI: 10.1161/CIRCRESAHA.111.242610]

13 **Schiavetta A**, Maione C, Botti C, Marino G, Lillo S, Garrone A, Lanza L, Pagliari S, Silvestroni A, Signoriello G, Sica V, Cobellis G. A phase II trial of autologous transplantation of bone marrow stem cells for critical limb ischemia: results of the Naples and Pietra Ligure Evaluation of Stem Cells study. *Stem Cells Transl Med* 2012; **1**: 572-578 [PMID: 23197862 DOI: 10.5966/sctm.2012-0021]

14 **Gupta PK**, Chullikana A, Parakh R, Desai S, Das A, Gottipamula S, Krishnamurthy S, Anthony N, Pherwani A, Majumdar AS. A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cell in critical limb ischemia. *J Transl Med* 2013; **11**: 143 [PMID: 23758736 DOI: 10.1186/1479-5876-11-143]

15 **Lunde K**, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, Egeland T, Endresen K, Ilebekk A, Mangschau A, Fjeld JG, Smith HJ, Taraldsrud E, Grøgaard HK, Bjørnerheim R, Brekke M, Müller C, Hopp E, Ragnarsson A, Brinchmann JE, Forfang K. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med* 2006; **355**: 1199-1209 [PMID: 16990383 DOI: 10.1056/NEJMoa055706]

16 **Traverse JH**, Henry TD, Ellis SG, Pepine CJ, Willerson JT, Zhao DX, Forder JR, Byrne BJ, Hatzopoulos AK, Penn MS, Perin EC, Baran KW, Chambers J, Lambert C, Raveendran G, Simon DI, Vaughan DE, Simpson LM, Gee AP, Taylor DA, Cogle CR, Thomas JD, Silva GV, Jorgenson BC, Olson RE, Bowman S, Francescon J, Geither C, Handberg E, Smith DX, Baraniuk S, Piller LB, Loghin C, Aguilar D, Richman S, Zierold C, Bettencourt J, Sayre SL, Vojvodic RW, Skarlatos SI, Gordon DJ, Ebert RF, Kwak M, Moyé LA, Simari RD. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA* 2011; **306**: 2110-2119 [PMID: 22084195 DOI: 10.1001/jama.2011.1670]

17 **Fraser JK**, Wulur I, Alfonso Z, Hedrick MH. Fat tissue: an underappreciated source of stem cells for biotechnology. *Trends Biotechnol* 2006; **24**: 150-154 [PMID: 16488036 DOI: 10.1016/j.tibtech.2006.01.010]

18 **Niemeyer P**, Kornacker M, Mehlhorn A, Seckinger A, Vohrer J, Schmal H, Kasten P, Eckstein V, Südkamp NP, Krause U. Comparison of immunological properties of bone marrow stromal cells and adipose tissue-derived stem cells before and after osteogenic differentiation in vitro. *Tissue Eng* 2007; **13**: 111-121 [PMID: 17518585 DOI: 10.1089/ten.2006.0114]

19 **Alipour F**, Parham A, Kazemi Mehrjerdi H, Dehghani H. Equine adipose-derived mesenchymal stem cells: phenotype and growth characteristics, gene expression profile and differentiation potentials. *Cell J* 2015; **16**: 456-465 [PMID: 25685736]

20 **Planells Roig MV**, Pallas Regueria JA, Carbonell Tatay F, Sancho Fornos S. Immune thrombocytopenia and HIV-1 infection. Response to splenectomy. *Rev Esp Enferm Dig* 1990; **77**: 225-226 [PMID: 2198906 DOI: 10.1186/1479-5876-5-55]

21 **Mitchell JB**, McIntosh K, Zvonic S, Garrett S, Floyd ZE, Kloster A, Di Halvorsen Y, Storms RW, Goh B, Kilroy G, Wu X, Gimble JM. Immunophenotype of human adipose-derived cells: temporal changes in stromal-associated and stem cell-associated markers. *Stem Cells* 2006; **24**: 376-385 [PMID: 16322640 DOI: 10.1634/stemcells.2005-0234]

22 **Bai X**, Alt E. Myocardial regeneration potential of adipose tissue-derived stem cells. *Biochem Biophys Res Commun* 2010; **401**: 321-326 [PMID: 20833143 DOI: 10.1016/j.bbrc.2010.09.012]

23 **Paul A**, Nayan M, Khan AA, Shum-Tim D, Prakash S. Angiopoietin-1-expressing adipose stem cells genetically modified with baculovirus nanocomplex: investigation in rat heart with acute infarction. *Int J Nanomedicine* 2012; **7**: 663-682 [PMID: 22334788 DOI: 10.2147/IJN.S26882]

24 **Shi CZ**, Zhang XP, Lv ZW, Zhang HL, Xu JZ, Yin ZF, Yan YQ, Wang CQ. Adipose tissue-derived stem cells embedded with eNOS restore cardiac function in acute myocardial infarction model. *Int J Cardiol* 2012; **154**: 2-8 [PMID: 21640405 DOI: 10.1016/j.ijcard.2011.05.078]

25 **Berardi GR**, Rebelatto CK, Tavares HF, Ingberman M, Shigunov P, Barchiki F, Aguiar AM, Miyague NI, Francisco JC, Correa A, Senegaglia AC, Suss PH, Moutinho JA, Sotomaior VS, Nakao LS, Brofman PS. Transplantation of SNAP-treated adipose tissue-derived stem cells improves cardiac function and induces neovascularization after myocardium infarct in rats. *Exp Mol Pathol* 2011; **90**: 149-156 [PMID: 21111728 DOI: 10.1016/j.yexmp.2010.11.005]

26 **Zuk PA**, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 2001; **7**: 211-228 [PMID: 11304456 DOI: 10.1089/107632701300062859]

27 **Lee RH**, Kim B, Choi I, Kim H, Choi HS, Suh K, Bae YC, Jung JS. Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue. *Cell Physiol Biochem* 2004; **14**: 311-324 [PMID: 15319535 DOI: 10.1159/000080341]

28 **Dicker A**, Le Blanc K, Aström G, van Harmelen V, Götherström C, Blomqvist L, Arner P, Rydén M. Functional studies of mesenchymal stem cells derived from adult human adipose tissue. *Exp Cell Res* 2005; **308**: 283-290 [PMID: 15925364 DOI: 10.1016/j.yexcr.2005.04.029]

29 **Wagner W**, Wein F, Seckinger A, Frankhauser M, Wirkner U, Krause U, Blake J, Schwager C, Eckstein V, Ansorge W, Ho AD. Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood. *Exp Hematol* 2005; **33**: 1402-1416 [PMID: 16263424 DOI: 10.1016/j.exphem.2005.07.003]

30 **Miranville A**, Heeschen C, Sengenès C, Curat CA, Busse R, Bouloumié A. Improvement of postnatal neovascularization by human adipose tissue-derived stem cells. *Circulation* 2004; **110**: 349-355 [PMID: 15238461 DOI: 10.1161/01.CIR.0000135466.16823.D0]

31 **Planat-Benard V**, Silvestre JS, Cousin B, André M, Nibbelink M, Tamarat R, Clergue M, Manneville C, Saillan-Barreau C, Duriez M, Tedgui A, Levy B, Pénicaud L, Casteilla L. Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives. *Circulation* 2004; **109**: 656-663 [PMID: 14734516 DOI: 10.1161/01.CIR.0000114522.38265.61]

32 **Rodríguez LV**, Alfonso Z, Zhang R, Leung J, Wu B, Ignarro LJ. Clonogenic multipotent stem cells in human adipose tissue differentiate into functional smooth muscle cells. *Proc Natl Acad Sci USA* 2006; **103**: 12167-12172 [PMID: 16880387 DOI: 10.1073/pnas.0604850103]

33 **Jeon ES**, Moon HJ, Lee MJ, Song HY, Kim YM, Bae YC, Jung JS, Kim JH. Sphingosylphosphorylcholine induces differentiation of human mesenchymal stem cells into smooth-muscle-like cells through a TGF-beta-dependent mechanism. *J Cell Sci* 2006; **119**: 4994-5005 [PMID: 17105765 DOI: 10.1242/jcs.03281]

34 **Rangappa S**, Fen C, Lee EH, Bongso A, Sim EK. Transformation of adult mesenchymal stem cells isolated from the fatty tissue into cardiomyocytes. *Ann Thorac Surg* 2003; **75**: 775-779 [PMID: 12645692 DOI: 10.1016/S0003-4975(02)04568-X]

35 **Gaustad KG**, Boquest AC, Anderson BE, Gerdes AM, Collas P. Differentiation of human adipose tissue stem cells using extracts of rat cardiomyocytes. *Biochem Biophys Res Commun* 2004; **314**: 420-427 [PMID: 14733922 DOI: 10.1016/j.bbrc.2003.12.109]

36 **Planat-Bénard V**, Menard C, André M, Puceat M, Perez A, Garcia-Verdugo JM, Pénicaud L, Casteilla L. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. *Circ Res* 2004; **94**: 223-229 [PMID: 14656930 DOI: 10.1161/01.RES.0000109792.43271.47]

37 **Valina C**, Pinkernell K, Song YH, Bai X, Sadat S, Campeau RJ, Le Jemtel TH, Alt E. Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function, perfusion, and remodelling after acute myocardial infarction. *Eur Heart J* 2007; **28**: 2667-2677 [PMID: 17933755 DOI: 10.1093/eurheartj/ehm426]

38 **Jack GS**, Almeida FG, Zhang R, Alfonso ZC, Zuk PA, Rodríguez LV. Processed lipoaspirate cells for tissue engineering of the lower urinary tract: implications for the treatment of stress urinary incontinence and bladder reconstruction. *J Urol* 2005; **174**: 2041-2045 [PMID: 16217390 DOI: 10.1097/01.ju.0000176489.96993.84]

39 **Strem BM**, Zhu M, Alfonso Z, Daniels EJ, Schreiber R, Beygui R, MacLellan WR, Hedrick MH, Fraser JK. Expression of cardiomyocytic markers on adipose tissue-derived cells in a murine model of acute myocardial injury. *Cytotherapy* 2005; **7**: 282-291 [PMID: 16081355 DOI: 10.1080/14653240510027226]

40 **Yamada Y**, Wang XD, Yokoyama S, Fukuda N, Takakura N. Cardiac progenitor cells in brown adipose tissue repaired damaged myocardium. *Biochem Biophys Res Commun* 2006; **342**: 662-670 [PMID: 16488397 DOI: 10.1016/j.bbrc.2006.01.181]

41 **Alvarez-Dolado M**, Pardal R, Garcia-Verdugo JM, Fike JR, Lee HO, Pfeffer K, Lois C, Morrison SJ, Alvarez-Buylla A. Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes. *Nature* 2003; **425**: 968-973 [PMID: 14555960 DOI: 10.1038/nature02069]

42 **Bai X**, Yan Y, Song YH, Seidensticker M, Rabinovich B, Metzele R, Bankson JA, Vykoukal D, Alt E. Both cultured and freshly isolated adipose tissue-derived stem cells enhance cardiac function after acute myocardial infarction. *Eur Heart J* 2010; **31**: 489-501 [PMID: 20037143 DOI: 10.1093/eurheartj/ehp568]

43 **Metzele R**, Alt C, Bai X, Yan Y, Zhang Z, Pan Z, Coleman M, Vykoukal J, Song YH, Alt E. Human adipose tissue-derived stem cells exhibit proliferation potential and spontaneous rhythmic contraction after fusion with neonatal rat cardiomyocytes. *FASEB J* 2011; **25**: 830-839 [PMID: 21059751 DOI: 10.1096/fj.09-153221]

44 **Rehman J**, Traktuev D, Li J, Merfeld-Clauss S, Temm-Grove CJ, Bovenkerk JE, Pell CL, Johnstone BH, Considine RV, March KL. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation* 2004; **109**: 1292-1298 [PMID: 14993122 DOI: 10.1161/01.CIR.0000121425.42966.F1]

45 **Nakagami H**, Maeda K, Morishita R, Iguchi S, Nishikawa T, Takami Y, Kikuchi Y, Saito Y, Tamai K, Ogihara T, Kaneda Y. Novel autologous cell therapy in ischemic limb disease through growth factor secretion by cultured adipose tissue-derived stromal cells. *Arterioscler Thromb Vasc Biol* 2005; **25**: 2542-2547 [PMID: 16224047 DOI: 10.1161/01.ATV.0000190701.92007.6d]

46 **Sadat S**, Gehmert S, Song YH, Yen Y, Bai X, Gaiser S, Klein H, Alt E. The cardioprotective effect of mesenchymal stem cells is mediated by IGF-I and VEGF. *Biochem Biophys Res Commun* 2007; **363**: 674-679 [PMID: 17904522 DOI: 10.1016/j.bbrc.2007.09.058]

47 **Yeghiazarians Y**, Zhang Y, Prasad M, Shih H, Saini SA, Takagawa J, Sievers RE, Wong ML, Kapasi NK, Mirsky R, Koskenvuo J, Minasi P, Ye J, Viswanathan MN, Angeli FS, Boyle AJ, Springer ML, Grossman W. Injection of bone marrow cell extract into infarcted hearts results in functional improvement comparable to intact cell therapy. *Mol Ther* 2009; **17**: 1250-1256 [PMID: 19384293 DOI: 10.1038/mt.2009.85]

48 **Bhang SH**, Lee S, Shin JY, Lee TJ, Jang HK, Kim BS. Efficacious and clinically relevant conditioned medium of human adipose-derived stem cells for therapeutic angiogenesis. *Mol Ther* 2014; **22**: 862-872 [PMID: 24413377 DOI: 10.1038/mt.2013.301]

49 **Albersen M**, Fandel TM, Lin G, Wang G, Banie L, Lin CS, Lue TF. Injections of adipose tissue-derived stem cells and stem cell lysate improve recovery of erectile function in a rat model of cavernous nerve injury. *J Sex Med* 2010; **7**: 3331-3340 [PMID: 20561166 DOI: 10.1111/j.1743-6109.2010.01875.x]

50 **Mazo M**, Planat-Bénard V, Abizanda G, Pelacho B, Léobon B, Gavira JJ, Peñuelas I, Cemborain A, Pénicaud L, Laharrague P, Joffre C, Boisson M, Ecay M, Collantes M, Barba J, Casteilla L, Prósper F. Transplantation of adipose derived stromal cells is associated with functional improvement in a rat model of chronic myocardial infarction. *Eur J Heart Fail* 2008; **10**: 454-462 [PMID: 18436478 DOI: 10.1016/j.ejheart.2008.03.017]

51 **Cai L**, Johnstone BH, Cook TG, Tan J, Fishbein MC, Chen PS, March KL. IFATS collection: Human adipose tissue-derived stem cells induce angiogenesis and nerve sprouting following myocardial infarction, in conjunction with potent preservation of cardiac function. *Stem Cells* 2009; **27**: 230-237 [PMID: 18772313 DOI: 10.1634/stemcells.2008-0273]

52 **Bagó JR**, Soler-Botija C, Casaní L, Aguilar E, Alieva M, Rubio N, Bayes-Genis A, Blanco J. Bioluminescence imaging of cardiomyogenic and vascular differentiation of cardiac and subcutaneous adipose tissue-derived progenitor cells in fibrin patches in a myocardium infarct model. *Int J Cardiol* 2013; **169**: 288-295 [PMID: 24157237 DOI: 10.1016/j.ijcard.2013.09.013]

53 **Rigol M**, Solanes N, Roura S, Roqué M, Novensà L, Dantas AP, Martorell J, Sitges M, Ramírez J, Bayés-Genís A, Heras M. Allogeneic adipose stem cell therapy in acute myocardial infarction. *Eur J Clin Invest* 2014; **44**: 83-92 [PMID: 24350923 DOI: 10.1111/eci.12195]

54 **Yin Q**, Pei Z, Wang H, Zhao Y. Cyclosporine A-nanoparticles enhance the therapeutic benefit of adipose tissue-derived stem cell transplantation in a swine myocardial infarction model. *Int J Nanomedicine* 2014; **9**: 17-26 [PMID: 24376353 DOI: 10.2147/IJN.S52005]

55 **Bayes-Genis A**, Soler-Botija C, Farré J, Sepúlveda P, Raya A, Roura S, Prat-Vidal C, Gálvez-Montón C, Montero JA, Büscher D, Izpisúa Belmonte JC. Human progenitor cells derived from cardiac adipose tissue ameliorate myocardial infarction in rodents. *J Mol Cell Cardiol* 2010; **49**: 771-780 [PMID: 20713059 DOI: 10.1016/j.yjmcc.2010.08.010]

56 **Danoviz ME**, Nakamuta JS, Marques FL, dos Santos L, Alvarenga EC, dos Santos AA, Antonio EL, Schettert IT, Tucci PJ, Krieger JE. Rat adipose tissue-derived stem cells transplantation attenuates cardiac dysfunction post infarction and biopolymers enhance cell retention. *PLoS One* 2010; **5**: e12077 [PMID: 20711471 DOI: 10.1371/journal.pone.0012077]

57 **Rigol M**, Solanes N, Farré J, Roura S, Roqué M, Berruezo A, Bellera N, Novensà L, Tamborero D, Prat-Vidal C, Huzman MA, Batlle M, Hoefsloot M, Sitges M, Ramírez J, Dantas AP, Merino A, Sanz G, Brugada J, Bayés-Genís A, Heras M. Effects of adipose tissue-derived stem cell therapy after myocardial infarction: impact of the route of administration. *J Card Fail* 2010; **16**: 357-366 [PMID: 20350704 DOI: 10.1016/j.cardfail.2009.12.006]

58 **Schenke-Layland K**, Strem BM, Jordan MC, Deemedio MT, Hedrick MH, Roos KP, Fraser JK, Maclellan WR. Adipose tissue-derived cells improve cardiac function following myocardial infarction. *J Surg Res* 2009; **153**: 217-223 [PMID: 18694573 DOI: 10.1016/j.jss.2008.03.019]

59 **Kim SW**, Lee DW, Yu LH, Zhang HZ, Kim CE, Kim JM, Park TH, Cha KS, Seo SY, Roh MS, Lee KC, Jung JS, Kim MH. Mesenchymal stem cells overexpressing GCP-2 improve heart function through enhanced angiogenic properties in a myocardial infarction model. *Cardiovasc Res* 2012; **95**: 495-506 [PMID: 22886775 DOI: 10.1093/cvr/cvs224]

60 **Okura H**, Saga A, Soeda M, Miyagawa S, Sawa Y, Daimon T, Ichinose A, Matsuyama A. Intracoronary artery transplantation of cardiomyoblast-like cells from human adipose tissue-derived multi-lineage progenitor cells improve left ventricular dysfunction and survival in a swine model of chronic myocardial infarction. *Biochem Biophys Res Commun* 2012; **425**: 859-865 [PMID: 22898045 DOI: 10.1016/j.bbrc.2012.08.004]

61 **Miyahara Y**, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, Hao H, Ishino K, Ishida H, Shimizu T, Kangawa K, Sano S, Okano T, Kitamura S, Mori H. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. *Nat Med* 2006; **12**: 459-465 [PMID: 16582917 DOI: 10.1038/nm1391]

62 **Okura H**, Matsuyama A, Lee CM, Saga A, Kakuta-Yamamoto A, Nagao A, Sougawa N, Sekiya N, Takekita K, Shudo Y, Miyagawa S, Komoda H, Okano T, Sawa Y. Cardiomyoblast-like cells differentiated from human adipose tissue-derived mesenchymal stem cells improve left ventricular dysfunction and survival in a rat myocardial infarction model. *Tissue Eng Part C Methods* 2010; **16**: 417-425 [PMID: 19624256 DOI: 10.1089/ten.TEC.2009.0362]

63 **Houtgraaf JH**, den Dekker WK, van Dalen BM, Springeling T, de Jong R, van Geuns RJ, Geleijnse ML, Fernandez-Aviles F, Zijlsta F, Serruys PW, Duckers HJ. First experience in humans using adipose tissue-derived regenerative cells in the treatment of patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2012; **59**: 539-540 [PMID: 22281257 DOI: 10.1016/j.jacc.2011.09.065]

64 **Perin EC**, Sanz-Ruiz R, Sánchez PL, Lasso J, Pérez-Cano R, Alonso-Farto JC, Pérez-David E, Fernández-Santos ME, Serruys PW, Duckers HJ, Kastrup J, Chamuleau S, Zheng Y, Silva GV, Willerson JT, Fernández-Avilés F. Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE Trial. *Am Heart J* 2014; **168**: 88-95.e2 [PMID: 24952864 DOI: 10.1016/j.ahj.2014.03.022]

65 **Lin YC**, Leu S, Sun CK, Yen CH, Kao YH, Chang LT, Tsai TH, Chua S, Fu M, Ko SF, Wu CJ, Lee FY, Yip HK. Early combined treatment with sildenafil and adipose-derived mesenchymal stem cells preserves heart function in rat dilated cardiomyopathy. *J Transl Med* 2010; **8**: 88 [PMID: 20868517 DOI: 10.1186/1479-5876-8-88]

66 **Hamdi H**, Boitard SE, Planat-Benard V, Pouly J, Neamatalla H, Joanne P, Perier MC, Bellamy V, Casteilla L, Li Z, Hagège AA, Mericskay M, Menasché P, Agbulut O. Efficacy of epicardially delivered adipose stroma cell sheets in dilated cardiomyopathy. *Cardiovasc Res* 2013; **99**: 640-647 [PMID: 23771945 DOI: 10.1093/cvr/cvt149]

67 **Pınarlı FA**, Turan NN, Pınarlı FG, Okur A, Sönmez D, Ulus T, Oğuz A, Karadeniz C, Delibaşı T. Resveratrol and adipose-derived mesenchymal stem cells are effective in the prevention and treatment of doxorubicin cardiotoxicity in rats. *Pediatr Hematol Oncol* 2013; **30**: 226-238 [PMID: 23363243 DOI: 10.3109/08880018.2012.762962]

68 **Harada Y**, Yamamoto Y, Tsujimoto S, Matsugami H, Yoshida A, Hisatome I. Transplantation of freshly isolated adipose tissue-derived regenerative cells enhances angiogenesis in a murine model of hind limb ischemia. *Biomed Res* 2013; **34**: 23-29 [PMID: 23428977 DOI: 10.2220/biomedres.34.23]

69 **Cao Y**, Sun Z, Liao L, Meng Y, Han Q, Zhao RC. Human adipose tissue-derived stem cells differentiate into endothelial cells in vitro and improve postnatal neovascularization in vivo. *Biochem Biophys Res Commun* 2005; **332**: 370-379 [PMID: 15896706 DOI: 10.1016/j.bbrc.2005.04.135]

70 **Moon MH**, Kim SY, Kim YJ, Kim SJ, Lee JB, Bae YC, Sung SM, Jung JS. Human adipose tissue-derived mesenchymal stem cells improve postnatal neovascularization in a mouse model of hindlimb ischemia. *Cell Physiol Biochem* 2006; **17**: 279-290 [PMID: 16791003 DOI: 10.1159/000094140]

71 **Cai L**, Johnstone BH, Cook TG, Liang Z, Traktuev D, Cornetta K, Ingram DA, Rosen ED, March KL. Suppression of hepatocyte growth factor production impairs the ability of adipose-derived stem cells to promote ischemic tissue revascularization. *Stem Cells* 2007; **25**: 3234-3243 [PMID: 17901400 DOI: 10.1634/stemcells.2007-0388]

72 **Sumi M**, Sata M, Toya N, Yanaga K, Ohki T, Nagai R. Transplantation of adipose stromal cells, but not mature adipocytes, augments ischemia-induced angiogenesis. *Life Sci* 2007; **80**: 559-565 [PMID: 17157325 DOI: 10.1016/j.lfs.2006.10.020]

73 **Cho HH**, Kim YJ, Kim JT, Song JS, Shin KK, Bae YC, Jung JS. The role of chemokines in proangiogenic action induced by human adipose tissue-derived mesenchymal stem cells in the murine model of hindlimb ischemia. *Cell Physiol Biochem* 2009; **24**: 511-518 [PMID: 19910691 DOI: 10.1159/000257495]

74 **Kondo K**, Shintani S, Shibata R, Murakami H, Murakami R, Imaizumi M, Kitagawa Y, Murohara T. Implantation of adipose-derived regenerative cells enhances ischemia-induced angiogenesis. *Arterioscler Thromb Vasc Biol* 2009; **29**: 61-66 [PMID: 18974384 DOI: 10.1161/ATVBAHA.108.166496]

75 **Kang Y**, Park C, Kim D, Seong CM, Kwon K, Choi C. Unsorted human adipose tissue-derived stem cells promote angiogenesis and myogenesis in murine ischemic hindlimb model. *Microvasc Res* 2010; **80**: 310-316 [PMID: 20510252 DOI: 10.1016/j.mvr.2010.05.006]

76 **Lee HC**, An SG, Lee HW, Park JS, Cha KS, Hong TJ, Park JH, Lee SY, Kim SP, Kim YD, Chung SW, Bae YC, Shin YB, Kim JI, Jung JS. Safety and effect of adipose tissue-derived stem cell implantation in patients with critical limb ischemia: a pilot study. *Circ J* 2012; **76**: 1750-1760 [PMID: 22498564 DOI: 10.1253/circj.CJ-11-1135]

77 **Madonna R**, Taylor DA, Geng YJ, De Caterina R, Shelat H, Perin EC, Willerson JT. Transplantation of mesenchymal cells rejuvenated by the overexpression of telomerase and myocardin promotes revascularization and tissue repair in a murine model of hindlimb ischemia. *Circ Res* 2013; **113**: 902-914 [PMID: 23780385 DOI: 10.1161/CIRCRESAHA.113.301690]

78 **Kang SK**, Lee DH, Bae YC, Kim HK, Baik SY, Jung JS. Improvement of neurological deficits by intracerebral transplantation of human adipose tissue-derived stromal cells after cerebral ischemia in rats. *Exp Neurol* 2003; **183**: 355-366 [PMID: 14552877 DOI: 10.1016/S0014-4886(03)00089-X]

79 **Gutiérrez-Fernández M**, Rodríguez-Frutos B, Ramos-Cejudo J, Teresa Vallejo-Cremades M, Fuentes B, Cerdán S, Díez-Tejedor E. Effects of intravenous administration of allogenic bone marrow- and adipose tissue-derived mesenchymal stem cells on functional recovery and brain repair markers in experimental ischemic stroke. *Stem Cell Res Ther* 2013; **4**: 11 [PMID: 23356495 DOI: 10.1186/scrt159]

80 **Liu XL**, Zhang W, Tang SJ. Intracranial transplantation of human adipose-derived stem cells promotes the expression of neurotrophic factors and nerve repair in rats of cerebral ischemia-reperfusion injury. *Int J Clin Exp Pathol* 2014; **7**: 174-183 [PMID: 24427337]

81 **Gutiérrez-Fernández M**, Rodríguez-Frutos B, Ramos-Cejudo J, Otero-Ortega L, Fuentes B, Vallejo-Cremades MT, Sanz-Cuesta BE, Díez-Tejedor E. Comparison between xenogeneic and allogeneic adipose mesenchymal stem cells in the treatment of acute cerebral infarct: proof of concept in rats. *J Transl Med* 2015; **13**: 46 [PMID: 25637958 DOI: 10.1186/s12967-015-0406-3]

82 **Takahashi M**, Suzuki E, Oba S, Nishimatsu H, Kimura K, Nagano T, Nagai R, Hirata Y. Adipose tissue-derived stem cells inhibit neointimal formation in a paracrine fashion in rat femoral artery. *Am J Physiol Heart Circ Physiol* 2010; **298**: H415-H423 [PMID: 19940081 DOI: 10.1152/ajpheart.00391.2009]

83 **Takahashi M**, Suzuki E, Kumano S, Oba S, Sato T, Nishimatsu H, Kimura K, Nagano T, Hirata Y. Angiopoietin-1 mediates adipose tissue-derived stem cell-induced inhibition of neointimal formation in rat femoral artery. *Circ J* 2013; **77**: 1574-1584 [PMID: 23486192 DOI: 10.1253/circj.CJ-12-0930]

84 **Bavry AA**, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006; **119**: 1056-1061 [PMID: 17145250 DOI: 10.1016/j.amjmed.2006.01.023]

85 **Stone GW**, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007; **356**: 998-1008 [PMID: 17296824 DOI: 10.1056/NEJMoa067193]

86 **Jeong JO**, Han JW, Kim JM, Cho HJ, Park C, Lee N, Kim DW, Yoon YS. Malignant tumor formation after transplantation of short-term cultured bone marrow mesenchymal stem cells in experimental myocardial infarction and diabetic neuropathy. *Circ Res* 2011; **108**: 1340-1347 [PMID: 21493893 DOI: 10.1161/CIRCRESAHA.110.239848]

87 **Muehlberg FL**, Song YH, Krohn A, Pinilla SP, Droll LH, Leng X, Seidensticker M, Ricke J, Altman AM, Devarajan E, Liu W, Arlinghaus RB, Alt EU. Tissue-resident stem cells promote breast cancer growth and metastasis. *Carcinogenesis* 2009; **30**: 589-597 [PMID: 19181699 DOI: 10.1093/carcin/bgp036]

88 **Heo SC**, Lee KO, Shin SH, Kwon YW, Kim YM, Lee CH, Kim YD, Lee MK, Yoon MS, Kim JH. Periostin mediates human adipose tissue-derived mesenchymal stem cell-stimulated tumor growth in a xenograft lung adenocarcinoma model. *Biochim Biophys Acta* 2011; **1813**: 2061-2070 [PMID: 21855581 DOI: 10.1016/j.bbamcr.2011.08.004]

89 **Ji SQ**, Cao J, Zhang QY, Li YY, Yan YQ, Yu FX. Adipose tissue-derived stem cells promote pancreatic cancer cell proliferation and invasion. *Braz J Med Biol Res* 2013; **46**: 758-764 [PMID: 24068191 DOI: 10.1590/1414-431X20132907]

90 **Madonna R**, Renna FV, Cellini C, Cotellese R, Picardi N, Francomano F, Innocenti P, De Caterina R. Age-dependent impairment of number and angiogenic potential of adipose tissue-derived progenitor cells. *Eur J Clin Invest* 2011; **41**: 126-133 [PMID: 20874854 DOI: 10.1111/j.1365-2362.2010.02384.x]

91 **Choudhery MS**, Badowski M, Muise A, Pierce J, Harris DT. Donor age negatively impacts adipose tissue-derived mesenchymal stem cell expansion and differentiation. *J Transl Med* 2014; **12**: 8 [PMID: 24397850 DOI: 10.1186/1479-5876-12-8]

92 **Laschke MW**, Grässer C, Kleer S, Scheuer C, Eglin D, Alini M, Menger MD. Adipose tissue-derived microvascular fragments from aged donors exhibit an impaired vascularisation capacity. *Eur Cell Mater* 2014; **28**: 287-298 [PMID: 25340807]

93 **Cianfarani F**, Toietta G, Di Rocco G, Cesareo E, Zambruno G, Odorisio T. Diabetes impairs adipose tissue-derived stem cell function and efficiency in promoting wound healing. *Wound Repair Regen* ; **21**: 545-553 [PMID: 23627689 DOI: 10.1111/wrr.12051]

94 **Fortini C**, Cesselli D, Beltrami AP, Bergamin N, Caragnano A, Moretti L, Cecaro F, Aquila G, Rizzo P, Riberti C, Tavazzi L, Fucili A, Beltrami CA, Ferrari R. Alteration of Notch signaling and functionality of adipose tissue derived mesenchymal stem cells in heart failure. *Int J Cardiol* 2014; **174**: 119-126 [PMID: 24767126 DOI: 10.1016/j.ijcard.2014.03.173]

95 **Yamanaka S**, Yokote S, Yamada A, Katsuoka Y, Izuhara L, Shimada Y, Omura N, Okano HJ, Ohki T, Yokoo T. Adipose tissue-derived mesenchymal stem cells in long-term dialysis patients display downregulation of PCAF expression and poor angiogenesis activation. *PLoS One* 2014; **9**: e102311 [PMID: 25025381 DOI: 10.1371/journal.pone.0102311]

96 **Rasmussen JG**, Frøbert O, Pilgaard L, Kastrup J, Simonsen U, Zachar V, Fink T. Prolonged hypoxic culture and trypsinization increase the pro-angiogenic potential of human adipose tissue-derived stem cells. *Cytotherapy* 2011; **13**: 318-328 [PMID: 20795759 DOI: 10.3109/14653249.2010.506505]

97 **Yamamoto Y**, Fujita M, Tanaka Y, Kojima I, Kanatani Y, Ishihara M, Tachibana S. Low oxygen tension enhances proliferation and maintains stemness of adipose tissue-derived stromal cells. *Biores Open Access* 2013; **2**: 199-205 [PMID: 23741631 DOI: 10.1089/biores.2013.0004]

98 **Chung DJ**, Wong A, Hayashi K, Yellowley CE. Effect of hypoxia on generation of neurospheres from adipose tissue-derived canine mesenchymal stromal cells. *Vet J* 2014; **199**: 123-130 [PMID: 24252224 DOI: 10.1016/j.tvjl.2013.10.020]

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MINIREVIEWS

Early repolarization syndrome: A cause of sudden cardiac death

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Abstract

Early repolarization syndrome (ERS), demonstrated as J-point elevation on an electrocardiograph, was formerly thought to be a benign entity, but the recent studies have demonstrated that it can be linked to a considerable risk of life - threatening arrhythmias and sudden cardiac death (SCD). Early repolarization characteristics associated with SCD include high - amplitude J-point elevation, horizontal and/or down-slopping ST segments, and inferior and/or lateral leads location. The prevalence of ERS varies between 3% and 24%, depending on age, sex and J-point elevation (0.05 mV *vs* 0.1 mV) being the main determinants. ERS patients are sporadic and they are at a higher risk of having recurrent cardiac events. Implantable cardioverter-defibrillator implantation and isoproterenol are the suggested therapies in this set of patients. On the other hand, asymptomatic patients with ERS are common and have a better prognosis. The risk stratification in asymptomatic patients with ERS still remains a grey area. This review provides an outline of the up-to-date evidence associated with ERS and the risk of life - threatening arrhythmias. Further prospective studies are required to elucidate the mechanisms of ventricular arrhythmogenesis in patients with ERS.

Key words: Early repolarization syndrome; Early repolarization; Sudden cardiac death; J-wave

Core tip: Early repolarization syndrome (ERS), demonstrated as J-point elevation on an electrocardiograph, was formerly thought to be a benign entity, but the recent studies have demonstrated that it can be linked to a higher risk of ventricular arrhythmias and sudden cardiac death. The prevalence of ERS varies between 3% and 24%, depending on age, sex and J-point elevation (0.05 mV *vs* 0.1 mV) being the main determinants. ERS patients are sporadic and they are at a higher risk of having recurrent cardiac events. Implantable cardioverter-defibrillator implantation and isoproterenol are the suggested therapies in this set of patients. On the other hand, asymptomatic patients with ERS are common and have a better prognosis. The risk stratification in asymptomatic patients with ERS still remains a grey area. This review provides an outline of the up-to-date evidence associated with ERS and the

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INTRODUCTION

Sudden cardiac death (SCD) is defined as natural death due to cardiac causes in a person who may or may not have previously recognized heart disease but in whom the time and mode of death are unexpected[1]. In the context of time, "sudden" is defined for most clinical and epidemiologic purposes as 1 h or less between a change in clinical status heralding the onset of the terminal clinical event and the cardiac arrest itself[1]. The overwhelming majority of SCD cases are related to cardiac arrhythmias[2]. The commonest electrophysiologic mechanisms leading to SCD are ventricular arrhythmias. About 10% of the cases of SCD are related to primary electrophysiological disorders with known (*e.g.*, Brugada syndrome) or unknown (*e.g.*, idiopathic VF) ion-channel abnormalities[1,3-8].

Early repolarization (ER), also recognized as "J-waves" or "J-point elevation"' is an electrocardiographic abnormality consistent with elevation of the junction between the end of the QRS complex and the beginning of the ST segment in 2 contiguous leads[9,10]. Grant *et al*[11] are considered to be the first who used the term ER to describe ST-segment deviations and related T wave inversion and premature repolarization was thought to be the underlying aetiology.

The so - called "early repolarization syndrome (ERS)" was unanimously and indisputably regarded as "normal," a "normal variant", or a "benign early repolarization" until 2000[12]. However, numerous more recent reports have suggested a relationship between ER and an increased risk of death from cardiac arrhythmias[8,13-19].

ERS is an electrocardiographic (ECG) entity characterized by J-point elevation manifested either as either QRS slurring (at the transition from the QRS segment to the ST-segment) or notching (a positive deflection inscribed on terminal S wave), ST segment elevation with upper concavity and prominent T-waves in at least two contiguous leads[20] (Figure 1).

PREVALENCE

The ERS is commonly seen in athletes, cocaine users, hypertrophic obstructive cardiomyopathy and defects and/or hypertrophy of interventricular septal defects[21-24]. Prevalence of ERS varies between 3% and 24% in the general population, depending on the population studied and methods used for ECG interpretation. Young individuals, especially those predisposed to vagotonia, males, African Americans, and athletes are subpopulations known to have a higher prevalence of ERS[19,20]. Tikkanen *et al*[13] demonstrated that the location (inferior *vs* lateral leads) as well as J-point elevation of > 0.2 mV are linked to a significant risk of death from cardiac arrhythmias (adjusted relative risk, 2.98; 95%CI: 1.85-4.92; $P < 0.001$).

HISTORICAL PERSPECTIVE

The J-deflection presenting as either QRS slurring or notching was first described in 1936 by Shilpey *et al*[25] and was considered a normal ECG variant. In 1938, Tomaszewski[26] presented the case of an accidently frozen man whose ECG demonstrated a very slowly inscribed deflection between the QRS complex and the earliest part of the ST segment, representing a J wave. In 1953, Osborn[27] described a "current of injury" later named "the Osborn wave" in acidotic and hypothermic dogs at rectal temperatures < 25 ℃.

In 1961, Wasserburger *et al*[28] further defined ER as a 1-4 mm takeoff of the ST-segment at the end of the QRS complex with a distinct notch or slur on the downslope of the R wave in the mid to left precordial leads.

In 1999, Gussak *et al*[29] suggested that ER may be malignant in some cases, based on observations that an ER pattern in arterial perfused wedge preparations can easily convert to one which gives rise to polymorphic ventricular tachycardia.

In 2000, evidence supporting above hypothesis was provided by Kalla *et al*[30] and Takagi *et al*[31]; they reported VF in patients with prominent J-wave and ST segment elevation in inferior leads without structural heart diseases and postulated that idiopathic VF with an ER pattern in inferior leads may represent a variant of the Brugada syndrome. In 2008, Haïssaguerre *et al*[8] and Nam *et al*[32] described a strong relationship between J-waves and many different forms of ventricular arrhythmias in the absence of known heart disease.

CELLULAR, MOLECULAR AND GENETIC CONSIDERATIONS

The pathophysiologic basis of the ER is currently not fully understood. The most discussed hypothesis incriminates that this may be related to either an increased susceptibility or vulnerability to cardiac arrest in critical ischemic conditions such as acute coronary syndromes[33], or to subtle changes in the cardiac action potential[34]. ER in its simplest form occurs in early phase of the cardiac action potential and is caused by the cardiac transient outward potassium current (I_{to}). If a situation arises where there is a reduced density of the I_{to} channels in the endocardium compared with

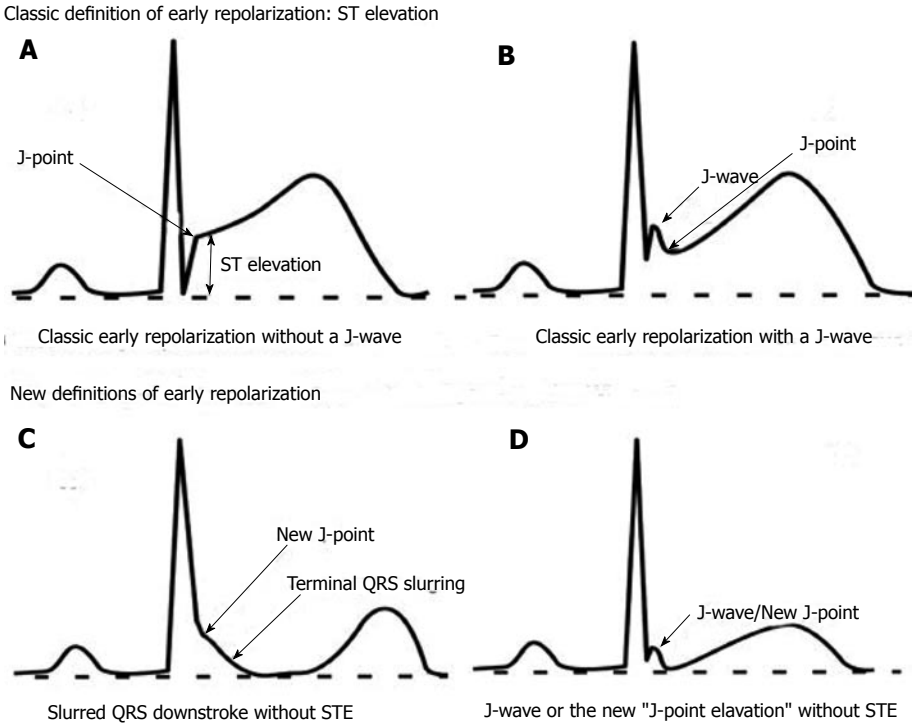

Figure 1 Examples of the classic and new definitions of early repolarization. Examples of the original (classic) and emerging (new) definitions of early repolarization (ER). A and B show the classic form of STE-type ER, which is the form identified by ECG software algorithms. Notice the presence of a J wave in (B), followed by an ascending/upsloping ST segment. Both forms are considered benign; C and D show the malignant form of ER demonstrated as slurring at the end of QRS complex (C) or a discrete notch/J wave (D) followed by a horizontal/downslopping ST segment (no ST elevation). Reproduced from ref.[49], with permission from the publisher. STE: ST elevation type ER; ECG: Electrocardiographic.

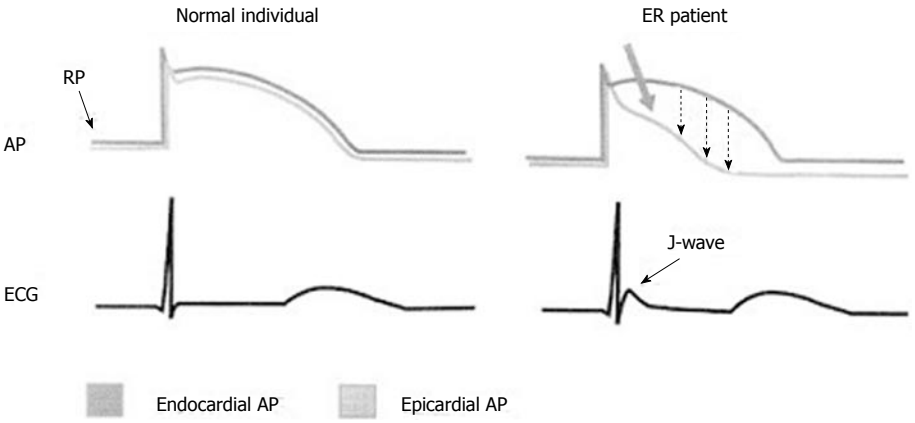

Figure 2 Schematic representation of the possible mechanisms underlying J-wave occurrence. Action potentials from epicardium and endocardium from normal individuals (left) and early repolarization (ER) patients (right) as well as the respective electrocardiograms are shown. A prominent phase I-notch and the loss of epicardial dome in phase - 2 (thick arrow) results in transmural dispersion of repolarization (dashed arrows) and appearance of the J-wave and ST-segment elevation on the surface ECG. AP: Action potential; ECG: Electrocardiogram; ER: Early repolarization; RP: Resting potention. Reproduced with permission, from ref.[67].

epicardium or mid-myocardium[35], a large Ito current can occur that results in electrocardiographic ER and large voltage gradients that may generate J wave elevation (Figure 2) and have the propensity to initiate life threatening arrhythmias[34,35].

Another hypothesis regarding the mechanism causing ER suggests an association of localized depolarization abnormalities with repolarization anomalies, as it happens in type 1 Brugada syndrome[36-39].

The genetic basis of ER syndrome continues to be elucidated, with the evidence restricted to either case reports or preliminary studies that fall short of clearly identifying the genetic basis of ER[40,41]. The reported implicated gene mutations involve the *KCNJ8* gene (responsible for the ATP sensitive potassium channel Kir6.1 - I_{KATP} current), *CACNA1C*, *CACNB2*, *CACNA2D1* genes (responsible for the cardiac L-type calcium channel - $I_{Ca.L}$ current), and the *SCN5A* gene (responsible for the sodium channel - I_{Na} current)[40-44]. All of these might enhance the underlying inward – outward current imbalance responsible for accelerated epicardial repolarization.

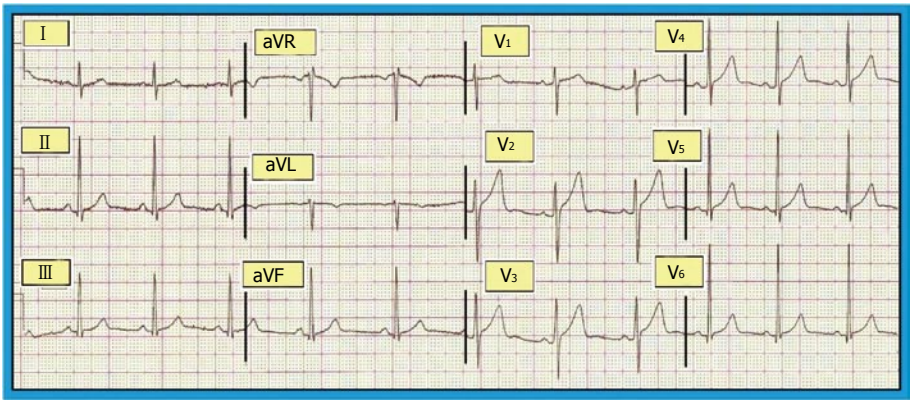

Figure 3 Benign early repolarization: Electrocardiogram showing ST segment elevation by at least 0.1 mV from the baseline. Reproduced with permission, from ref.[68].

CLINICAL MANIFESTATIONS OF ERS

The clinical presentation of patients with ERS can be subdivided into two main groups. The first includes those that manifest recognized symptoms of ERS, *i.e.*, high risk patients with syncope and survivors of cardiac arrest[45]. A study by Abe *et al*[46] demonstrated that the ER was noticed in 18.5% in patients with syncope compared to 2% in healthy controls, this equates to almost 10 - fold increase risk of syncope in patients with ERS. Although very rare, this group is highly likely to have recurrent cardiac events. In his study, Haissaguerre demonstrated 41% risk of arrhythmia recurrences in this cohort, when he followed up 64 ERS patients for a median of 51 mo[8].

The second and the most common group are asymptomatic patients who are incidentally noted to have an ER pattern on their ECG[8]. Overall, this group is less likely to have adverse cardiac events, and the challenge here lies in distinguishing those with risk of sudden cardiac death from those that are likely to run a benign course of the condition[47,48].

ECG DIAGNOSIS OF ERS

The electrocardiographic hallmark of ERS is elevation (> 1 mm above baseline) of the QRS - ST junction manifested as either QRS slurring or notching, ST-segment elevation with upper concavity, and prominent T-waves in two or more contiguous inferior and/or lateral leads in a patient resuscitated from otherwise unexplained ventricular arrhythmia[20]. Recent studies omitted ST segment elevation from the definition of ERS, and state that the J point changes described above is sufficient to diagnose ERS[49]. The inclusion or exclusion of right precordial leads is also an area for debate. Haïssaguerre *et al*[8] argue that in order to differentiate ERS from Brugada Syndrome, right precordial leads should be excluded, while others state that, the distinction is less straightforward. The latter group are backed by recent data pointing out the similarities in mechanism, overlapping genetic predisposition and the clinical findings of both conditions. Indeed, the term "J-Wave Syndrome" has been suggested to describe ERS and Brugada Syndrome as a spectrum of a clinical condition[36].

Antzelevitch *et al*[36] described three subtypes of ERS, and highlighted a pattern of risk profile: (1) type 1: It shows ER in the lateral precordial leads that is seen in healthy male athletes and has the lowest risk of malignant arrhythmias (Figure 3); (2) type 2: It shows ER in the inferior and inferolateral leads and is associated with a greater risk of malignant arrhythmias; and (3) type 3: It shows ER pattern in all ECG leads (Figure 4) and has the highest risk of malignant arrhythmias and electrical storms.

The Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) consensus statement on the diagnosis and management of primary inherited arrhythmia syndromes recommended criteria for the diagnosis of ER is shown in Table 1[50].

DIFFERENTIAL DIAGNOSIS

Early Repolarisation syndrome have a wide differential including Brugada Syndrome, short and long QT syndromes as well as other conditions causing ST segment elevation (ST segment elevation MI, acute pericarditis and idiopathic VF). Brugada sydnrome (BS), perhaps the closest clinical entity to ERS, is a primary repolarisation disorder characterized by a prominent J-wave causing a pattern of incomplete right bundle branch block and ST-segment elevation in the right precordial leads (V1-V3) (Figure 5) and significant risk of sudden cardiac death in individuals with no known structural heart disease[51]. BS, an autosomal dominant condition, is more common in males and has a variable penetrance[52,53]. Symptoms of BS include syncope with or without any warning signs, seizures and nocturnal agonal respiration; however, ECG remains the cornerstone of diagnosis of BS[54]. However, the Brugada ECG feature of provocation by sodium channel blocker is not observed in ER[55]. In fact, sodium channel blockers in most patients with ER

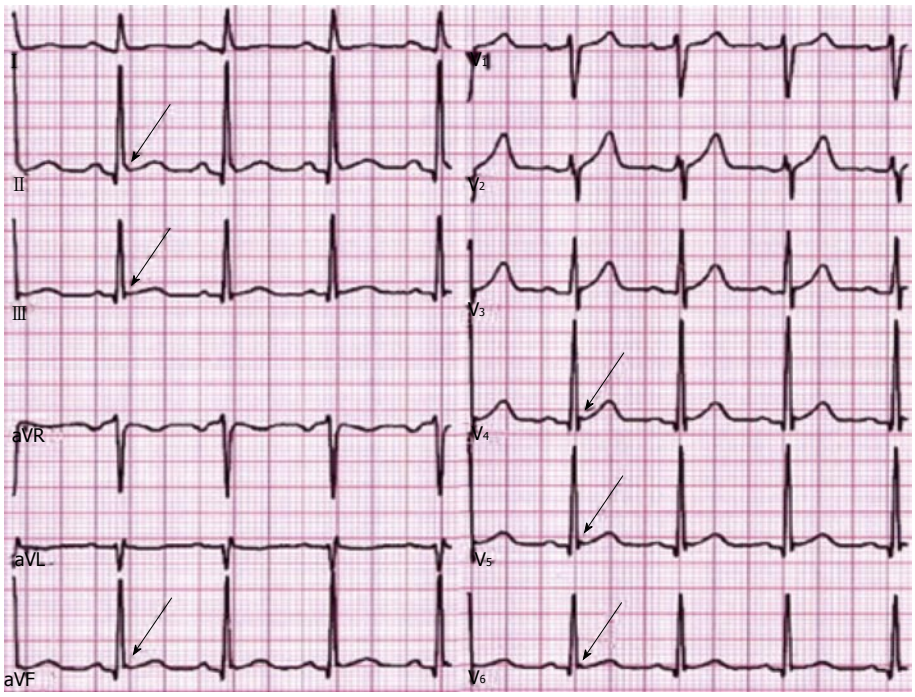

Figure 4 Malignant early repolarization: J-wave elevation (arrows) as slurring (lead II) and notching in the inferior and lateral leads and ascending ST segment in most leads. Reproduced with permission, from ref.[69].

Table 1 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society consensus statement on the diagnosis and management of primary inherited arrhythmia syndromes recommended criteria for the diagnosis of early repolarization

ER expert consensus recommendations on early repolarization diagnosis
ER syndrome is diagnosed in the presence of J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT
ER syndrome can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
ER pattern can be diagnosed in the presence of J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

ER: Early repolarization; ECG: Electrocardiogram; SCD: Sudden cardiac death. Reproduced from ref.[50], with permission from the publisher.

attenuate the J-point, whereas the J-point is augmented by sodium-channel blockers in the right precordial leads in patients with a Brugada ECG.

In acute pericarditis, there is J-point elevation with resultant ST segment elevation, as seen in ER. Symptom presentation is distinctly different in the two conditions. Unlike ER, most patients with acute pericarditis have ST elevations diffusely in most or all limb and precordial leads. Additionally, patients with acute pericarditis often have deviation of the PR segment, which is not present in ER.

While patients with acute myocardial injury due to ST elevation myocardial infarction (STEMI) can initially have J-point elevation with concave ST segment elevation, the ST segment elevation typically becomes more pronounced and convex (rounded upward) as the infarction persists. However, the primary distinguishing factor between ER and acute myocardial injury is the presence of clinical symptoms such as chest pain or dyspnoea. ER and notching of the terminal QRS need to be considered in risk stratification for arrhythmias in patients with coronary artery disease and after coronary artery bypass grafting.

Table 2 gives a list of conditions with J-wave on the ECG.

BENIGN OR MALIGNANT

The identification of high-risk patients with ERS remains challenging. Currently, surface ECG is the only available tool in order to differentiate between the benign and the malignant forms of ERS. A horizontal or descending ST-segment elevation has been associated with adverse outcomes (compared with a rapidly ascending ST-segment elevation) following J-point elevation[56,57]. The extent of the J-point elevation may also have prognostic implication: a slurred or notched J-point elevation ≥ 2 mm (0.2 mV) appears to be associated with a higher risk[13,57]. Other abnormalities, such as localization of the ER pattern in inferior or inferolateral (compared with lateral) leads[3] or extension of ER into a BrS pattern, may also represent a worse prognosis[19,58,59].

The benign type of ERS is commonly associated with young age group, left ventricular hypertrophy on ECG,

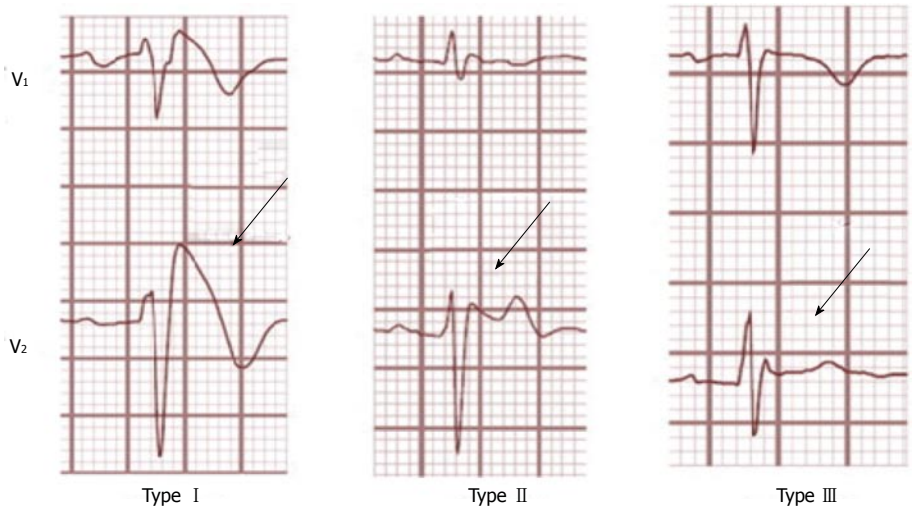

Figure 5 Brugada electrocardiogram-types. Type-1 is characterized by a complete or incomplete right bundle-branch block pattern with a coved morphology ST-segment elevation of ≥ 2 mm in the right precordial leads (V1-V3) followed by a negative T-wave. In type-2, ST-segment elevation has a saddleback appearance with a high takeoff ST-segment elevation of > 2 mm, a trough displaying > 1-mm ST-elevation followed by a positive or biphasic T-wave. Type-3 has an ST-segment morphology that is either saddleback or coved with an ST-segment elevation of < 1 mm. Reproduced with permission, from ref.[69].

Table 2 Conditions with J-wave on the electrocardiogram

Conditions with predominant J-waves
Hypothermia
Hypercalcaemia
Hyperkalaemia
Vasospastic angina
Brugada syndrome
Early repolarization syndrome
Short QT syndrome
Hypoxia
Acidosis
Pulmonary embolism
Arrhythmogenic right ventricular cardiomyopathy
Subarachnoid haemorrhage

Reproduced from ref.[50], with permission from the publisher.

lower blood pressure and lower heart rate, which are all features of healthy, physically active individuals. On the other hand, the malignant form of ERS, characterized by horizontal or descending ST-segment variation (Figure 6), is associated with older individuals and ECGs suggestive of ischaemic heart disease[60].

It appears that the morphology of the ST-segment could help in distinguishing "benign" from "malignant ER"[57]; nonetheless, there is no way to know who would be at considerable risk when presenting with slurring or notching of the QRS unless they have had a cardiac arrest[34].

TREATMENT

The ER pattern is a benign incidental finding, without any specific signs or symptoms attributed to it. There is no current risk stratification strategy for asymptomatic patients with ER pattern in general population and within families with ER pattern that would allow for identification of higher risk individuals with the ER pattern who might be candidates for treatment. The current consensus is that these patients do not require specific investigations or therapeutic interventions[28].

Among the survivors of SCD due to idiopathic VF, the reported rate of recurrent VF ranges between 22% and 37% at two to four years[6]. Because these patients have no structural heart disease, they have an excellent prognosis for long-term survival if VF is treated. As a result, such patients are best treated with an implantable cardioverter-defibrillator (ICD)[6,60-63]. HRS/EHRA/APHRS consensus statement on the diagnosis and management of primary inherited arrhythmia syndromes recommendations for therapeutic interventions in ERS are shown in Table 3[50].

It has been demonstrated that patients with VF and ER have a higher prevalence of recurrence of VF than VF patients without ER (43% *vs* 23%, $P < 0.001$) during a five years follow-up[8]. In a multicenter observational cohort study of 122 patients (90 males, mean age 37 ± 12 years) with ER in the inferolateral leads and more than three episodes of idiopathic VF (including those with electrical storm), isoproterenol was effective for the acute suppression of VF, immediately suppressing electrical storms in seven of seven patients[64]. In terms of long term therapy, VF recurrences have been demonstrated to be effectively suppressed by quinidine therapy[64]. Encouraging results recently emerged from a study by Gurabi *et al*[65], who demonstrated that in addition to quinidine, cilostazol, and milrinone suppress the hypothermia - induced VT/VF in a canine left ventricular model.

However, there exists a "gray area" in between the two ends of the spectrum, where no clear guidelines exist. Examples include patients with syncope who may have a "malignant" ER pattern and/or a significant family history of sudden cardiac death. The current guidelines suggest that ICD implantation may be

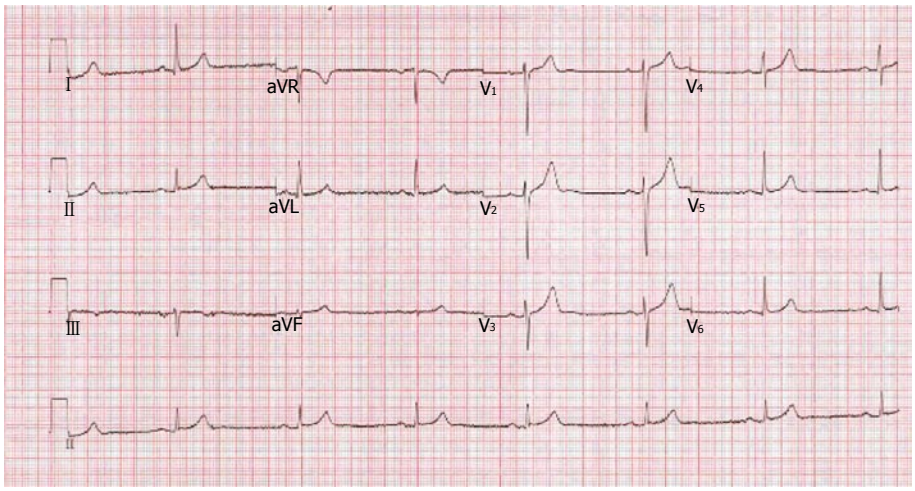

Figure 6 Malignant early repolarization: Horizontal ST-segment after early repolarization.

Table 3 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society consensus statement on the diagnosis and management of primary inherited arrhythmia syndromes recommendations for therapeutic interventions in early repolarization syndrome

Expert consensus recommendations on early repolarization therapeutic interventions		
Class Ⅰ	1	ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest
Class Ⅱa	2	Isoproterenol infusion can be useful in suppressing electrical storms in patients with a diagnosis of ER syndrome
	3	Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ER syndrome
Class Ⅱb	4	ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation > 1 mm in 2 or more inferior or lateral leads
	5	ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/descending ST segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation
Class Ⅲ	6	ICD implantation is not recommended in asymptomatic patients with an isolated ER ECG pattern

ER: Early repolarization; ECG: Electrocardiogram; ICD: Implantable cardioverter-defibrillator.

considered in high-risk individuals with unexplained syncope[50].

SCREENING FAMILY MEMBERS

There are no current recommendations can be given to do ECG screening of the families of individuals with asymptomatic ER pattern or individuals with strong family history of ER or ER with VF. There are no recognized provocative tests that would help in diagnosing concealed ER in family members of patients with ERS, although preliminary observation advocate that concealed ER cases may be recognized by Valsalva maneurve[50,66].

CONCLUSION

In the recent years, ER syndrome has been associated with a significant risk of life - threatening arrhythmias and cardiac death. It is currently not possible to identify asymptomatic individual patients with ER who are at a higher risk of having cardiac arrhythmias with any clinically useful degree of accuracy. It is also not possible to identify asymptomatic individuals with a primary arrhythmogenic disorder attributable to ER. All patients with ER should continue to have modifiable cardiac risk factors addressed.

Until we have a better knowledge, physicians are left with the observation that in patients with ER in the inferolateral leads, life-threatening ventricular arrhythmias may occur and may lead to sudden cardiac death. Since there are a large number of patients who fit such a criteria but do not appear to have excess risk of arrhythmias, further data is needed to reveal how to identify the group of patients who would be at a significant risk and what measures can be taken to prevent it.

REFERENCES

1 **Brugada J**, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 1998; **97**: 457-460 [PMID: 9490240 DOI: 10.1161/01.CIR.97.5.457]
2 **Zipes DP**, Wellens HJ. Sudden cardiac death. *Circulation* 1998; **98**: 2334-2351 [PMID: 9826323]
3 **Moss AJ**, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: a prospective international study. *Circulation* 1985; **71**: 17-21 [PMID: 2856865 DOI: 10.1161/01.CIR.71.1.17]
4 **Gaita F**, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT Syndrome: a familial cause of sudden death. *Circulation* 2003; **108**: 965-970 [PMID:

12925462 DOI: 10.1161/01.CIR.0000085071.28695.C4]
5 **Corrado D**, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. *Cardiovasc Res* 2001; **50**: 399-408 [PMID: 11334844 DOI: 10.1016/S0008-6363(01)00254-1]
6 **Viskin S**, Belhassen B. Idiopathic ventricular fibrillation. *Am Heart J* 1990; **120**: 661-671 [PMID: 2202193 DOI: 10.1016/0002-8703(90)90025-S]
7 **Huikuri HV**, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001; **345**: 1473-1482 [PMID: 11794197 DOI: 10.1056/NEJMra000650]
8 **Haïssaguerre M**, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008; **358**: 2016-2023 [PMID: 18463377 DOI: 10.1056/NEJMoa071968]
9 **Klatsky AL**, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. *Am J Med* 2003; **115**: 171-177 [PMID: 12935822 DOI: 10.1016/S0002-9343(03)00355-3]
10 **Mehta M**, Jain AC, Mehta A. Early repolarization. *Clin Cardiol* 1999; **22**: 59-65 [PMID: 10068841 DOI: 10.1002/clc.4960220203]
11 **Grant RP**, Estes EH, Doyle JT. Spatial vector electrocardiography; the clinical characteristics of S-T and T vectors. *Circulation* 1951; **3**: 182-197 [PMID: 14812646 DOI: 10.1161/01.CIR.3.2.182]
12 **Gussak I**, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. *J Electrocardiol* 2000; **33**: 299-309 [PMID: 11099355 DOI: 10.1054/jelc.2000.18106]
13 **Tikkanen JT**, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009; **361**: 2529-2537 [PMID: 19917913 DOI: 10.1056/NEJMoa0907589]
14 **Rosso R**, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol* 2008; **52**: 1231-1238 [PMID: 18926326 DOI: 10.1016/j.jacc.2008.07.010]
15 **Sinner MF**, Reinhard W, Müller M, Beckmann BM, Martens E, Perz S, Pfeufer A, Winogradow J, Stark K, Meisinger C, Wichmann HE, Peters A, Riegger GA, Steinbeck G, Hengstenberg C, Kääb S. Association of early repolarization pattern on ECG with risk of cardiac and all-cause mortality: a population-based prospective cohort study (MONICA/KORA). *PLoS Med* 2010; **7**: e1000314 [PMID: 20668657 DOI: 10.1371/journal.pmed.1000314]
16 **Haruta D**, Matsuo K, Tsuneto A, Ichimaru S, Hida A, Sera N, Imaizumi M, Nakashima E, Maemura K, Akahoshi M. Incidence and prognostic value of early repolarization pattern in the 12-lead electrocardiogram. *Circulation* 2011; **123**: 2931-2937 [PMID: 21646495 DOI: 10.1161/CIRCULATIONAHA.110.006460]
17 **Olson KA**, Viera AJ, Soliman EZ, Crow RS, Rosamond WD. Long-term prognosis associated with J-point elevation in a large middle-aged biracial cohort: the ARIC study. *Eur Heart J* 2011; **32**: 3098-3106 [PMID: 21785106 DOI: 10.1093/eurheartj/ehr264]
18 **Abe A**, Ikeda T, Tsukada T, Ishiguro H, Miwa Y, Miyakoshi M, Mera H, Yusu S, Yoshino H. Circadian variation of late potentials in idiopathic ventricular fibrillation associated with J waves: insights into alternative pathophysiology and risk stratification. *Heart Rhythm* 2010; **7**: 675-682 [PMID: 20189495 DOI: 10.1016/j.hrthm.2010.01.023]
19 **Nam GB**, Ko KH, Kim J, Park KM, Rhee KS, Choi KJ, Kim YH, Antzelevitch C. Mode of onset of ventricular fibrillation in patients with early repolarization pattern vs. Brugada syndrome. *Eur Heart J* 2010; **31**: 330-339 [PMID: 19880418 DOI: 10.1093/eurheartj/ehp423]
20 **Miyazaki S**, Shah AJ, Haïssaguerre M. Early repolarization syndrome - a new electrical disorder associated with sudden cardiac death. *Circ J* 2010; **74**: 2039-2044 [PMID: 20838009 DOI: 10.1253/circj.CJ-10-0753]
21 **Serra-Grima R**, Doñate M, Álvarez-García J, Barradas-Pires A, Ferrero A, Carballeira L, Puig T, Rodríguez E, Cinca J. Long-term follow-up of early repolarization pattern in elite athletes. *Am J Med* 2015; **128**: 192.e1-192.e9 [PMID: 24979742 DOI: 10.1016/j.amjmed.2014.06.017]
22 **Barbosa EC**, Bomfim Ade S, Benchimol-Barbosa PR, Ginefra P. Ionic mechanisms and vectorial model of early repolarization pattern in the surface electrocardiogram of the athlete. *Ann Noninvasive Electrocardiol* 2008; **13**: 301-307 [PMID: 18713332 DOI: 10.1111/j.1542-474X.2008.00235.x]
23 **Biasco L**, Cristoforetti Y, Castagno D, Giustetto C, Astegiano P, Ganzit G, Gribaudo CG, Gaita F. Clinical, electrocardiographic, echocardiographic characteristics and long-term follow-up of elite soccer players with J-point elevation. *Circ Arrhythm Electrophysiol* 2013; **6**: 1178-1184 [PMID: 24097373 DOI: 10.1161/CIRCEP.113.000434]
24 **Quattrini FM**, Pelliccia A, Assorgi R, DiPaolo FM, Squeo MR, Culasso F, Castelli V, Link MS, Maron BJ. Benign clinical significance of J-wave pattern (early repolarization) in highly trained athletes. *Heart Rhythm* 2014; **11**: 1974-1982 [PMID: 25092400 DOI: 10.1016/j.hrthm.2014.07.042]
25 **Shilpey R**, Hallaran W. The four lead electrogram in 200 normal men and women. *Am Heart J* 1936; **11**: 325–345 [DOI: 10.1016/S0002-8703(36)90417-9]
26 **Tomaszewski W**. Changement electrocardiographiques observes chez un home mort de froid. *Arch Mal Coeur Vaiss* 1938; **31**: 525-528
27 **Osborn JJ**. Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. *Am J Physiol* 1953; **175**: 389-398 [PMID: 13114420]
28 **Wasserburger RH**, Alt WJ. The normal RS-T segment elevation variant. *Am J Cardiol* 1961; **8**: 184-192 [PMID: 13783301 DOI: 10.1016/0002-9149(61)90204-1]
29 **Gussak I**, Antzelevitch C, Bjerregaard P, Towbin JA, Chaitman BR. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. *J Am Coll Cardiol* 1999; **33**: 5-15 [PMID: 9935001 DOI: 10.1016/S0735-1097(98)00528-2]
30 **Kalla H**, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant? *J Cardiovasc Electrophysiol* 2000; **11**: 95-98 [PMID: 10695469 DOI: 10.1111/j.1540-8167.2000.tb00743.x]
31 **Takagi M**, Aihara N, Takaki H, Taguchi A, Shimizu W, Kurita T, Suyama K, Kamakura S. Clinical characteristics of patients with spontaneous or inducible ventricular fibrillation without apparent heart disease presenting with J wave and ST segment elevation in inferior leads. *J Cardiovasc Electrophysiol* 2000; **11**: 844-848 [PMID: 10969745 DOI: 10.1111/j.1540-8167.2000.tb00062.x]
32 **Nam GB**, Kim YH, Antzelevitch C. Augmentation of J waves and electrical storms in patients with early repolarization. *N Engl J Med* 2008; **358**: 2078-2079 [PMID: 18463391 DOI: 10.1056/NEJMc0708182]
33 **Tikkanen JT**, Wichmann V, Junttila MJ, Rainio M, Hookana E, Lappi OP, Kortelainen ML, Anttonen O, Huikuri HV. Association of early repolarization and sudden cardiac death during an acute coronary event. *Circ Arrhythm Electrophysiol* 2012; **5**: 714-718 [PMID: 22730409 DOI: 10.1161/CIRCEP.112.978585]
34 **Benito B**, Guasch E, Rivard L, Nattel S. Clinical and mechanistic issues in early repolarization of normal variants and lethal arrhythmia syndromes. *J Am Coll Cardiol* 2010; **56**: 1177-1186 [PMID: 20883924]
35 **Li GR**, Lau CP, Ducharme A, Tardif JC, Nattel S. Transmural action potential and ionic current remodeling in ventricles of failing canine hearts. *Am J Physiol Heart Circ Physiol* 2002; **283**: H1031-H1041 [PMID: 12181133 DOI: 10.1152/ajpheart.00105.2002]
36 **Antzelevitch C**, Yan GX. J wave syndromes. *Heart Rhythm* 2010; **7**: 549-558 [PMID: 20153265 DOI: 10.1016/j.hrthm.2009.12.006]
37 **Yan GX**, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular

repolarization components on the electrocardiogram: cellular basis and clinical significance. *J Am Coll Cardiol* 2003; **42**: 401-409 [PMID: 12906963 DOI: 10.1016/S0735-1097(03)00713-7]

38 **Gussak I**, George S, Bojovic B, Vajdic B. ECG phenomena of the early ventricular repolarization in the 21 century. *Indian Pacing Electrophysiol J* 2008; **8**: 149-157 [PMID: 18679530]

39 **Boineau JP**. The early repolarization variant--an electrocardiographic enigma with both QRS and J-STT anomalies. *J Electrocardiol* 2007; **40**: 3.e1-3.10 [PMID: 17074359 DOI: 10.1016/j.jelectrocard.2006.05.001]

40 **Haïssaguerre M**, Chatel S, Sacher F, Weerasooriya R, Probst V, Loussouarn G, Horlitz M, Liersch R, Schulze-Bahr E, Wilde A, Kääb S, Koster J, Rudy Y, Le Marec H, Schott JJ. Ventricular fibrillation with prominent early repolarization associated with a rare variant of KCNJ8/KATP channel. *J Cardiovasc Electrophysiol* 2009; **20**: 93-98 [PMID: 19120683 DOI: 10.1111/j.1540-8167.2008.01326.x]

41 **Watanabe H**, Nogami A, Ohkubo K, Kawata H, Hayashi Y, Ishikawa T, Makiyama T, Nagao S, Yagihara N, Takehara N, Kawamura Y, Sato A, Okamura K, Hosaka Y, Sato M, Fukae S, Chinushi M, Oda H, Okabe M, Kimura A, Maemura K, Watanabe I, Kamakura S, Horie M, Aizawa Y, Shimizu W, Makita N. Electrocardiographic characteristics and SCN5A mutations in idiopathic ventricular fibrillation associated with early repolarization. *Circ Arrhythm Electrophysiol* 2011; **4**: 874-881 [PMID: 22028457 DOI: 10.1161/CIRCEP.111.963983]

42 **Medeiros-Domingo A**, Tan BH, Crotti L, Tester DJ, Eckhardt L, Cuoretti A, Kroboth SL, Song C, Zhou Q, Kopp D, Schwartz PJ, Makielski JC, Ackerman MJ. Gain-of-function mutation S422L in the KCNJ8-encoded cardiac K(ATP) channel Kir6.1 as a pathogenic substrate for J-wave syndromes. *Heart Rhythm* 2010; **7**: 1466-1471 [PMID: 20558321 DOI: 10.1016/j.hrthm.2010.06.016]

43 **Barajas-Martínez H**, Hu D, Ferrer T, Onetti CG, Wu Y, Burashnikov E, Boyle M, Surman T, Urrutia J, Veltmann C, Schimpf R, Borggrefe M, Wolpert C, Ibrahim BB, Sánchez-Chapula JA, Winters S, Haïssaguerre M, Antzelevitch C. Molecular genetic and functional association of Brugada and early repolarization syndromes with S422L missense mutation in KCNJ8. *Heart Rhythm* 2012; **9**: 548-555 [PMID: 22056721 DOI: 10.1016/j.hrthm.2011.10.035]

44 **Burashnikov E**, Pfeiffer R, Barajas-Martinez H, Delpón E, Hu D, Desai M, Borggrefe M, Häissaguerre M, Kanter R, Pollevick GD, Guerchicoff A, Laiño R, Marieb M, Nademanee K, Nam GB, Robles R, Schimpf R, Stapleton DD, Viskin S, Winters S, Wolpert C, Zimmern S, Veltmann C, Antzelevitch C. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm* 2010; **7**: 1872-1882 [PMID: 20817017 DOI: 10.1016/j.hrthm.2010.08.026]

45 **Aizawa Y**, Chinushi M, Hasegawa K, Naiki N, Horie M, Kaneko Y, Kurabayashi M, Ito S, Imaizumi T, Aizawa Y, Takatsuki S, Joo K, Sato M, Ebe K, Hosaka Y, Haissaguerre M, Fukuda K. Electrical storm in idiopathic ventricular fibrillation is associated with early repolarization. *J Am Coll Cardiol* 2013; **62**: 1015-1019 [PMID: 23747791 DOI: 10.1016/j.jacc.2013.05.030]

46 **Abe A**, Yoshino H, Ishiguro H, Tsukada T, Miwa Y, Sakaki K. Prevalence of J waves in 12-lead electrocardiogram in patients with syncope and no organic disorder. *J Cardiovasc Electrophysiol* 2007; **18**: S88

47 **Rosso R**, Halkin A, Viskin S. J waves and early repolarization: do not confuse me with the facts! *Heart Rhythm* 2012; **9**: 1603-1604 [PMID: 22842117 DOI: 10.1016/j.hrthm.2012.07.019]

48 **Viskin S**, Rosso R, Halkin A. Making sense of early repolarization. *Heart Rhythm* 2012; **9**: 566-568 [PMID: 22120134 DOI: 10.1016/j.hrthm.2011.11.042]

49 **Perez MV**, Friday K, Froelicher V. Semantic confusion: the case of early repolarization and the J point. *Am J Med* 2012; **125**: 843-844 [PMID: 22340816 DOI: 10.1016/j.amjmed.2011.08.024]

50 **Priori SG**, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm* 2013; **10**: e85-108 [PMID: 23916535]

51 **Brugada P**, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992; **20**: 1391-1396 [PMID: 1309182 DOI: 10.1016/0735-1097(92)90253-J]

52 **Watanabe H**, Koopmann TT, Le Scouarnec S, Yang T, Ingram CR, Schott JJ, Demolombe S, Probst V, Anselme F, Escande D, Wiesfeld AC, Pfeufer A, Kääb S, Wichmann HE, Hasdemir C, Aizawa Y, Wilde AA, Roden DM, Bezzina CR. Sodium channel β1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest* 2008; **118**: 2260-2268 [PMID: 18464934 DOI: 10.1172/jci33891]

53 **Antzelevitch C**, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005; **111**: 659-670 [PMID: 15655131 DOI: 10.1161/01.CIR.0000152479.54298.51]

54 **Sarkozy A**, Chierchia GB, Paparella G, Boussy T, De Asmundis C, Roos M, Henkens S, Kaufman L, Buyl R, Brugada R, Brugada J, Brugada P. Inferior and lateral electrocardiographic repolarization abnormalities in Brugada syndrome. *Circ Arrhythm Electrophysiol* 2009; **2**: 154-161 [PMID: 19808460 DOI: 10.1161/CIRCEP.108.795153]

55 **Kawata H**, Noda T, Yamada Y, Okamura H, Satomi K, Aiba T, Takaki H, Aihara N, Isobe M, Kamakura S, Shimizu W. Effect of sodium-channel blockade on early repolarization in inferior/lateral leads in patients with idiopathic ventricular fibrillation and Brugada syndrome. *Heart Rhythm* 2012; **9**: 77-83 [PMID: 21855521 DOI: 10.1016/j.hrthm.2011.08.017]

56 **Tikkanen JT**, Junttila MJ, Anttonen O, Aro AL, Luttinen S, Kerola T, Sager SJ, Rissanen HA, Myerburg RJ, Reunanen A, Huikuri HV. Early repolarization: electrocardiographic phenotypes associated with favorable long-term outcome. *Circulation* 2011; **123**: 2666-2673 [PMID: 21632493 DOI: 10.1161/CIRCULATIONAHA.110.014068]

57 **Rosso R**, Glikson E, Belhassen B, Katz A, Halkin A, Steinvil A, Viskin S. Distinguishing "benign" from "malignant early repolarization": the value of the ST-segment morphology. *Heart Rhythm* 2012; **9**: 225-229 [PMID: 21914497 DOI: 10.1016/j.hrthm.2011.09.012]

58 **Kawata H**, Morita H, Yamada Y, Noda T, Satomi K, Aiba T, Isobe M, Nagase S, Nakamura K, Fukushima Kusano K, Ito H, Kamakura S, Shimizu W. Prognostic significance of early repolarization in inferolateral leads in Brugada patients with documented ventricular fibrillation: a novel risk factor for Brugada syndrome with ventricular fibrillation. *Heart Rhythm* 2013; **10**: 1161-1168 [PMID: 23587501 DOI: 10.1016/j.hrthm.2013.04.009]

59 **Tokioka K**, Kusano KF, Morita H, Miura D, Nishii N, Nagase S, Nakamura K, Kohno K, Ito H, Ohe T. Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities. *J Am Coll Cardiol* 2014; **63**: 2131-2138 [PMID: 24703917 DOI: 10.1016/j.jacc.2014.01.072]

60 **Letsas KP**, Charalampous C, Korantzopoulos P, Tsikrikas S, Bramos D, Kollias G, Efremidis M, Sideris A. Novel indexes of heterogeneity of ventricular repolarization in subjects with early repolarization pattern. *Europace* 2012; **14**: 877-881 [PMID: 22186777 DOI: 10.1093/europace/eur390]

61 **Wever EF**, Hauer RN, Oomen A, Peters RH, Bakker PF, Robles de Medina EO. Unfavorable outcome in patients with primary electrical disease who survived an episode of ventricular fibrillation. *Circulation* 1993; **88**: 1021-1029 [PMID: 8353864 DOI: 10.1161/01.CIR.88.3.1021]

62 **Marcus FI**. Idiopathic ventricular fibrillation. *J Cardiovasc Electrophysiol* 1997; **8**: 1075-1083 [PMID: 9300306 DOI: 10.1111/j.1540-8167.1997.tb00632.x]

63 Survivors of out-of-hospital cardiac arrest with apparently normal heart. Need for definition and standardized clinical evaluation.

Consensus Statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. *Circulation* 1997; **95**: 265-272 [PMID: 8994445]

64 **Haïssaguerre M**, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, Mantovan R, Cappato R, Wolpert C, Leenhardt A, de Roy L, Heidbuchel H, Deisenhofer I, Arentz T, Pasquié JL, Weerasooriya R, Hocini M, Jais P, Derval N, Bordachar P, Clémenty J. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. *J Am Coll Cardiol* 2009; **53**: 612-619 [PMID: 19215837 DOI: 10.1016/j.jacc.2008.10.044]

65 **Gurabi Z**, Koncz I, Patocskai B, Nesterenko VV, Antzelevitch C. Cellular mechanism underlying hypothermia-induced ventricular tachycardia/ventricular fibrillation in the setting of early repolarization and the protective effect of quinidine, cilostazol, and milrinone. *Circ Arrhythm Electrophysiol* 2014; **7**: 134-142 [PMID: 24429494 DOI: 10.1161/CIRCEP.113.000919]

66 **Ackerman MJ**, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm* 2011; **8**: 1308-1339 [PMID: 21787999 DOI: 10.1016/j.hrthm.2011.05.020]

67 **Bronis K**, Kappas K, Manolis AS. Early repolarization: Not benign any more - The J-wave syndrome. *Hospital Chronicles* 2012; **7**: 215-228

68 Grauer K. ECG Blog #47. Available from: URL: http://tinyurl.com/KG-Blog-47

69 **Sethi KK**, Sethi K, Chutani SK. Early repolarisation and J wave syndromes. *Indian Heart J* 2014; **66**: 443-452 [PMID: 25173204 DOI: 10.1016/j.ihj.2014.06.002]

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MINIREVIEWS

Role of left ventricular twist mechanics in cardiomyopathies, dance of the helices

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Abstract

Left ventricular twist is an essential part of left ventricular function. Nevertheless, knowledge is limited in "the cardiology community" as it comes to twist mechanics. Fortunately the development of speckle tracking echocardiography, allowing accurate, reproducible and rapid bedside assessment of left ventricular twist, has boosted the interest in this important mechanical aspect of left ventricular deformation. Although the fundamental physiological role of left ventricular twist is undisputable, the clinical relevance of assessment of left ventricular twist in cardiomyopathies still needs to be established. The fact remains; analysis of left ventricular twist mechanics has already provided substantial pathophysiological understanding on a comprehensive variety of cardiomyopathies. It has become clear that increased left ventricular twist in for example hypertrophic cardiomyopathy may be an early sign of subendocardial (microvascular) dysfunction. Furthermore, decreased left ventricular twist may be caused by left ventricular dilatation or an extensive myocardial scar. Finally, the detection of left ventricular rigid body rotation in noncompaction cardiomyopathy may provide an indispensible method to objectively confirm this difficult diagnosis. All this endorses the value of left ventricular twist in the field of cardiomyopathies and may further encourage the implementation of left ventricular twist parameters in the "diagnostic toolbox" for cardiomyopathies.

Key words: Left ventricular mechanics; Left ventricular twist; Cardiomyopathy

Core tip: Left ventricular twist is an essential part of left ventricular function. Nevertheless, knowledge is limited in "the cardiology community" as it comes to twist mechanics. It has become clear that increased left ventricular twist in for example hypertrophic cardiomyopathy may be an early sign of subendocardial (microvascular) dysfunction. Furthermore, decreased left ventricular twist may be caused by left ventricular

dilatation or an extensive myocardial scar. Finally, the detection of left ventricular rigid body rotation in noncompaction cardiomyopathy may provide an indispensible method to objectively confirm this difficult diagnosis. All this endorses the value of left ventricular twist in the field of cardiomyopathies and may further encourage the implementation of left ventricular twist parameters in the "diagnostic toolbox" for cardiomyopathies.

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INTRODUCTION

As early as the 16th century Leonardo da Vinci[1,2] wrote about the twisting deformation of the heart and Richard Lower compared the myocardial contraction with "the wringing of a linen cloth to squeeze out the water" in his observations of myocardial contraction in 1669[3,4]. A complex spiral architecture is the mechanical basis for this wringing motion[5,6]. The left ventricle comprises of obliquely orientated multiple layers of cardiomyocytes, transforming from a subendocardially located (smaller-radius) right-handed helix to a subepicardial (larger-radius) left-handed helix.

This helix generates a torsional motion pattern caused by rotation in a clockwise direction (as seen from the apex) at the level of the mitral valve (basal level) and counter clockwise rotation of the apex (apical level). This twisting deformation performs a fundamental part in the mechanical efficiency of the heart resulting in a 60% ejection fraction with only 15% fibre shortening[7]. Furthermore, left ventricular untwisting is essential in actively aiding diastolic filling[8]. The physiology of left ventricular twist and changes of left ventricular twist in different cardiomyopathies are reviewed in this paper.

ASSESSMENT OF LEFT VENTRICULAR TWIST

By his first description of left ventricular twist, Leonardo da Vinci[1,2] has been a constant inspiration for scientists in their pursuit to comprehend the functioning of the human heart. Nevertheless, reliable quantitative measurement of left ventricular twist in a non-invasive manner has not been possible until recently.

Speckle tracking echocardiography is based on automated tracking of a specific portion of myocardial tissue being visualized by a pattern of gray values, a speckle pattern, on an ultrasound image. These gray values are the result of the analysis of the reflection of ultrasound interfering with the myocardial tissue. Therefore, movement of speckle patterns represent motion of myocardial tissue[9].

In case a of suitably high frame rate, the pattern of speckles is conserved from frame to frame[10]. By following a specific pattern of speckles, the motion of the corresponding myocardial segment can be tracked, thus allowing to quantify deformation of the myocardium and, as a function of time, deformation rate (Figure 1). Several validation studies[11,12] showed good correlation between left ventricular twist assessment by commercially available speckle tracking software and magnetic resonance imaging. Also, speckle tracking derived left ventricular twist has been shown to be feasible and reproducible, and may thereby be used as a method to follow-up patients[13].

PHYSIOLOGY OF LEFT VENTRICULAR TWIST

After the first description of left ventricular twist by Da Vinci, it lasted until the late 1960s before a more detailed description of twist was provided by Streeter *et al*[5] in a study of post-mortem canine hearts. Generally, myofibre position changes gradually from +60 degrees (circumferential axis as a reference) subendocardially to -60 degrees at the subepicardium. The counter coiled helix of subepi - and subendocardial fibres generates twist. The direction of basal and apical rotation is dominated by the larger - radius fibres at the subepicardium, caused by their longer arm of movement[14]. The significance of the direction of fibres has been demonstrated in patient studies as well[15]. Left ventricular twist showed a linear relation with sphericity index (as a measure of change in left ventricle fibre orientation, because in more spherically shaped hearts fibres are supposed to be oriented more horizontally) in patients with a dilated cardiomyopathy, supporting the hypothesis on twist mechanics and the influence of the direction of fibres on the twisting left ventricular deformation[14].

The influence of aging on twist was studied by several groups[16-19]. In all these studies, aging appeared to be related to an increase of left ventricular twist. As the function of the fibres at the subendocardium deteriorates when getting older, even in normal hearts[20,21], the reduction of the opposing rotational forces of the subendocardium will result in an increase of apical rotation by the already dominant subepicardial fibres and consequently in an increase of left ventricular twist. This increase of left ventricular twist appears to be a part of "physiological cardiac aging". One may hypothesize that this increase of twist contributes to the conservation of left ventricular stroke volume with ageing.

Untwisting begins after left ventricular twist reaches its peak, usually shortly before end-systole. Systolic twisting leads to storage of potential energy in the compressed coil of twisted fibres of the left

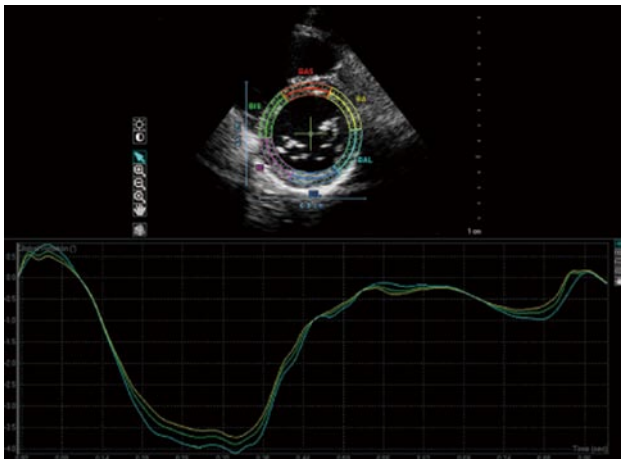

Figure 1 Example of QLAB workstation speckle-tracking analysis. Upper panel: 2D echo image of the basal left ventricular short axis. The software fully automatically draws the epicardial and endocardial contour of the myocardium. Lower panel: The software calculates the change in angle between the left ventricular (LV) wall and the virtual LV center during the cardiac cycle (green line). The blue and yellow line represent the angulation of the epicardial en endocardial angulation, respectively.

ventricular wall[19]. During isovolemic relaxation this coil springs open and releases this energy. Fibres at the subepicardium that are still depolarized and are at that time - in contrast to systole - not overruled by active contraction of the fibres located at the subepicardium, might dynamically reinforce this role of untwisting in diastole[19,22]. It was shown by magnetic resonance imaging that there is an important dissociation of time of untwist and filling, approximately 40% of the untwist takes place during isovolumic relaxation[23]. Furthermore, the extent of the diastolic intraventricular pressure gradient is strongly related to untwisting. Even more so, untwist precedes the development of this pressure gradient, thereby potentially being an important indicator of suction during early diastole[24,25].

TWIST MECHANICS IN CARDIOMYOPATHIES

Hypertrophic cardiomyopathy

Left ventricular twist in patients with hypertrophic cardiomyopathy is moderately increased, in particular the left ventricular basal rotation[26-29]. This augmented rotation at mitral valve level is probably caused by reduced counteraction of the subendocardial fibres, due to subendocardial ischemia caused by endocardial microvascular insufficiency and increased oxygen demand[30,31]. This is supported by the phenomenon of increased rotation being most pronounced in the hypertrophic segments[26]. A larger difference in radius between the subepicardium and subendocardium will increase the arm of effect on the already dominant fibres of the subepicardium and consequently will increase rotation at mitral valve level (basal rotation)[26].

There is a significant relation between the pattern of hypertrophy on apical rotation and twist. If the septum has a sigmoid curvature, rotation of the apex is more pronounced than in reverse septal curvature hearts. Outflow tract obstruction is more common in patients in whom the septum has a sigmoid curvature. The resulting intraventricular forces from these outflow tract gradients can lead to microvascular insufficiency and thereby to more (sub)endocardial ischemia. Subsequently, this lack of oxygen might cause impairment of the countereffect of contraction of the subendocardially located myocardial fibres on left ventricular twist.

The necessity to objectively demonstrate diastolic dysfunction in hypertrophic cardiomyopathy has caused an ongoing pursuit for a non invasive and load independent technique for quantifying the severity of diastolic dysfunction. For instance Takeuchi *et al*[32] examined the effect of left ventricular hypertrophy in hypertensive patients on untwisting of the left ventricle. In moderate to severe hypertrophy, untwisting was reduced and delayed as compared to healthy individuals, supposedly resulting in decreased function of left ventricular diastole. In hypertrophic cardiomyopathy[33] and also in aortic stenosis[34] the untwisting rate, being the mean untwisting velocity during the isovolumic relaxation phase, is decreased and as a result untwisting is delayed[27]. In hypertrophic cardiomyopathy this was most obvious in the affected segments[27,29]. Also, compromised elastic characteristics lead to suboptimal transformation of the potential kinetic energy stored in the twisted heart. Peak diastolic untwisting velocity is reduced in hypertrophic cardiomyopathy whereas it is augmented in aortic stenosis. In aortic stenosis twist is increased more severe. Release of the relatively high amount of potential energy results in increased untwisting, possibly compensating for otherwise diastolic dysfunction[27,35]. In hypertrophic cardiomyopathy twist is just discreetly increased, weakening this effect[27,33].

Dilated cardiomyopathy

Twist in non-ischaemic dilated left ventricles is known to be reduced. The abnormal shape of the left ventricle in dilated cardiomyopathy may cause a change in fibre orientation. This fibre orientation is of importance in left ventricular twist as described earlier. This influence was found as an independent linear relation between left ventricular sphericity index and peak systolic twist. The more dilated the left ventricle, the more decreased the left ventricular twist. Actually, also in patients with dilated cardiomyopathy and comparable left ventricular ejection fraction, sphericity index was still significantly related to left ventricular twist[15]. Nonetheless, derangement of myocardial fibre architecture is not the only cause for decreased left ventricular twist in patients with non-ischaemic dilated cardiomyopathy as fibrosis appeared to play a role in decreased left ventricular twist.

The extent of myocardial fibrosis in dilated cardiomyopathy has been evaluated by cardiac magnetic

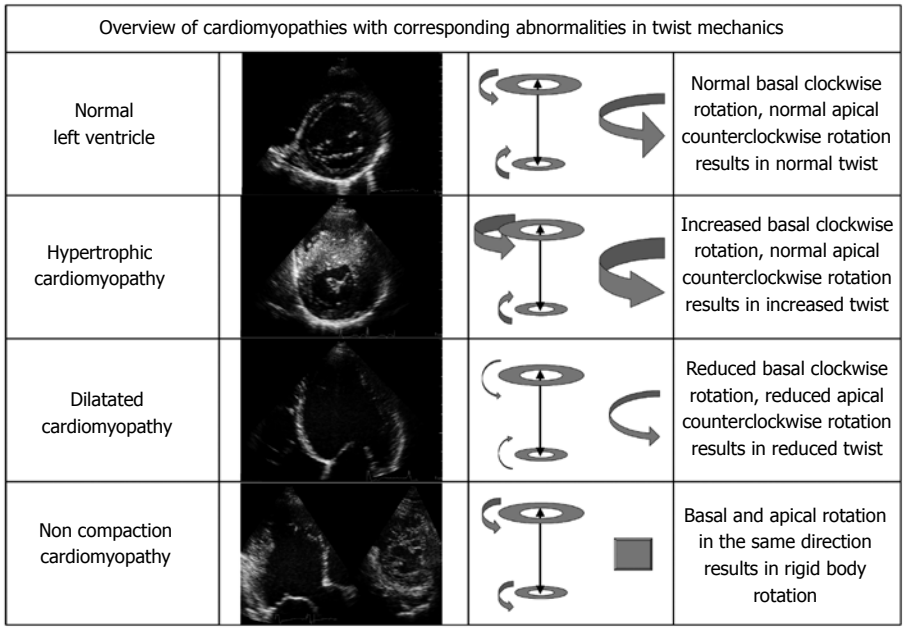

Figure 2 Overview of cardiomyopathies with corresponding abnormalities in left ventricular twist mechanics.

resonance imaging with late gadolinium enhancement. Fibrosis proved to be related to twist[36]. Reduction of twist indicated more extensive cardiac fibrosis.

As explained earlier, very rapid left ventricular untwisting is known to play a prominent part in fast filling in early diastole. However, in dilated hearts untwisting is delayed, leading to an apex-to-base-rotation delay. This will interfere with early diastolic suction and might harm filling of the left ventricle in dilated cardiomyopathy[27,37,38].

Noncompaction cardiomyopathy

Noncompaction cardiomyopathy is still subject to debate because of the shortcoming on consensus on its pathogenesis, diagnosis and treatment[39-41].

In the final embryonic development of the heart the myocardial tissue is transformed in a compact myocardium together with the formation of epicardial and endocardial fibre as oppositely wound helices[6,42]. As noncompaction cardiomyopathy is supposed to be caused by intrauterine arrest of cardiac embryogenesis during this transformation[43], distorted left ventricular twist features may be expected, even more than in the situation of reduced systolic function and a normally compacted myocardium. This was recognised in clinical studies[44-48] where noncompaction cardiomyopathy patients displayed a twist pattern with basal and apical rotation in the same direction, resulting in almost full absence of left ventricular twist. This rotation pattern is known as left ventricular rigid body rotation[44,49]. Rigid body rotation demonstrated, in a relative large study, to have a good predictive value for the diagnosis of noncompaction cardiomyopathy[47]. Even more interesting, all familial noncompaction cardiomyopathy patients showed rigid body rotation. The fact that noncompaction cardiomyopathy diagnosis is most definite in these patients underscores the good sensitivity of rigid body rotation in diagnosing noncompaction cardiomyopathy.

The clinical importance of left ventricular rigid body rotation was shown in more recent studies, where rigid body rotation was found in a majority of noncompaction cardiomyopathy patients as well[50,51], but the patients with rigid body rotation and noncompaction cardiomyopathy proved to have a lower NYHA functional status as compared to the patients without rigid body rotation[48].

Ischemic cardiomyopathy

An optical device attached to the apex was used in a canine model to study the early effects of myocardial ischemia[52]. Ischemia was inflicted by occluding the anterior descending coronary artery. Early after induction of ischemia, there was a paradoxical increase of apical rotation. This finding was ascribed to secluded ischemia of the subendocardium, resulting in a declined counteractive effect of the fibres located at the subendocardium[27,52].

Also, Moen *et al*[53] used speckle-tracking echocardiography on eight anesthetized pigs to define regional myocardial function in anterior wall ischemia. They discovered left ventricular twist remained normal until there was extensive impairment of perfusion of the left anterior descending artery.

Sun *et al*[54] induced a myocardial infarction in 7 pigs, leading to decreased twist, specifically in the area perfused by the occluded coronary artery[27,54]. Hence, it was suggested that twist might be used to assess wall motion abnormalities in order to localize cardiac ischemia. Conversely, in a clinical study using dobutamine stress echo in 125 patients with myocardial infarction or ischemia, the influence of myocardial infarction on left ventricular twist proved to be related

to size rather than localisation of infarction. In addition, stress-induced myocardial ischemia did not influence left ventricular twist[55]. Other studies on anterior myocardial infarction patients showed a decreased apical rotation in the infarcted left ventricle however with a preserved left ventricular basal rotation[56,57].

When left ventricular myocardial infarction was complicated by left ventricular aneurysm formation, rotation of the apex was lost or even reversed, consequently losing left ventricular twist. Restorative surgery as a treatment of this problem is rather complex: the aim is to reconstruct a near normal ventricular chamber after aneurysm formation and thus reducing left ventricular volume and improving ejection fraction[58]. Setser *et al*[59] did not see a significant improvement in their patients left ventricular twist after traditional left ventricular reconstruction. Much more interesting however; when an improved restoration technique was used, where residual myocardium around the defect was re-approached endeavouring to redirect fibre orientation displaced by infarct scar toward a more physiological gross disposition, left ventricular twist did improve in all patients[60]. This encouraging concept of fibre orientation based surgical reparative surgery, could expand the potential of repairing the failing heart.

CONCLUSION

Left ventricular twist is an essential part of left ventricular function. Nevertheless, knowledge is limited in "the cardiology community" as it comes to twist mechanics.

Fortunately, evolution of echocardiography, permitting speckle tracking to precisely assess left ventricular twist, has boosted the awareness of this fundamental feature of cardiac mechanics. The vital role of twist in the physiology of the heart is undisputable. Nevertheless, the significance of twist assessment in daily clinical practice in patients with a cardiomyopathy still has to be established[27]. On the other hand, twist analysis has contributed substantially to the understanding of pathophysiology in a diversity of cardiomyopathies (Figure 2). Increased twist in for example hypertrophic cardiomyopathy may be an early sign of subendocardial (microvascular) dysfunction. Furthermore, decreased twist might be initiated by left ventricular dilatation or an extensive myocardial scar. Finally, the detection of rigid body rotation in noncompaction cardiomyopathy could serve as an indispensible method to accurately diagnose this challenging entity. All this highlights the importance of left ventricular twist in the field of cardiomyopathies and may further encourage the implementation of left ventricular twist parameters in the "diagnostic toolbox" for cardiomyopathies[27].

REFERENCES

1 **Keele KD**. Leonardo da Vinci's elements of the science of man. New York, USA: Academic Press, 1983
2 **Da Vinci L**. Quoted by Evans l. Starling's Principles of Human Physiology. London, UK: J.A. Churchill, 1936: 706
3 **Lower R**. Tractus de corde. In: Gunter RT, editor. Early Science in Oxford. Oxford, London, UK: Sawsons, Pall Mall, 1968: 1169
4 **Geleijnse ML**, van Dalen BM. Let's twist. *Eur J Echocardiogr* 2009; **10**: 46-47 [PMID: 18801724 DOI: 10.1093/ejechocard/jen241]
5 **Streeter DD**, Spotnitz HM, Patel DP, Ross J, Sonnenblick EH. Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res* 1969; **24**: 339-347 [PMID: 5766515 DOI: 10.1161/01.RES.24.3.339]
6 **Greenbaum RA**, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981; **45**: 248-263 [PMID: 7008815 DOI: 10.1136/hrt.45.3.248]
7 **Sallin EA**. Fiber orientation and ejection fraction in the human left ventricle. *Biophys J* 1969; **9**: 954-964 [PMID: 5791550]
8 **Notomi Y**, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, Thomas JD. Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 2006; **113**: 2524-2533 [PMID: 16717149 DOI: 10.1161/CIRCULATIONAHA.105.596502]
9 **D'hooge J**. Principles and Different Techniques for Speckle Tracking, in Myocardial Imaging: Tissue Doppler and Speckle Tracking. Marwick TH, Yu CM, Sun JP, editors. Oxford, UK: Blackwell Publishing Ltd, 2007 [DOI: 10.1002/9780470692448.ch2]
10 **Ramamurthy BS**, Trahey GE. Potential and limitations of angle-independent flow detection algorithms using radio-frequency and detected echo signals. *Ultrason Imaging* 1991; **13**: 252-268 [PMID: 1957423 DOI: 10.1016/0161-7346(91)90075-S]
11 **Notomi Y**, Lysyansky P, Setser RM, Shiota T, Popović ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, Thomas JD. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol* 2005; **45**: 2034-2041 [PMID: 15963406 DOI: 10.1016/j.jacc.2005.02.082]
12 **Helle-Valle T**, Crosby J, Edvardsen T, Lyseggen E, Amundsen BH, Smith HJ, Rosen BD, Lima JA, Torp H, Ihlen H, Smiseth OA. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation* 2005; **112**: 3149-3156 [PMID: 16286606]
13 **van Dalen BM**, Soliman OI, Vletter WB, Kauer F, van der Zwaan HB, ten Cate FJ, Geleijnse ML. Feasibility and reproducibility of left ventricular rotation parameters measured by speckle tracking echocardiography. *Eur J Echocardiogr* 2009; **10**: 669-676 [PMID: 19383641]
14 **Taber LA**, Yang M, Podszus WW. Mechanics of ventricular torsion. *J Biomech* 1996; **29**: 745-752 [PMID: 9147971 DOI: 10.1016/0021-9290(95)00129-8]
15 **van Dalen BM**, Kauer F, Vletter WB, Soliman OI, van der Zwaan HB, Ten Cate FJ, Geleijnse ML. Influence of cardiac shape on left ventricular twist. *J Appl Physiol* (1985) 2010; **108**: 146-151 [PMID: 19850734]
16 **Nakai H**, Takeuchi M, Nishikage T, Kokumai M, Otani S, Lang RM. Effect of aging on twist-displacement loop by 2-dimensional speckle tracking imaging. *J Am Soc Echocardiogr* 2006; **19**: 880-885 [PMID: 16824997 DOI: 10.1016/j.echo.2006.02.007]
17 **Takeuchi M**, Nakai H, Kokumai M, Nishikage T, Otani S, Lang RM. Age-related changes in left ventricular twist assessed by two-dimensional speckle-tracking imaging. *J Am Soc Echocardiogr* 2006; **19**: 1077-1084 [PMID: 16950461]
18 **van Dalen BM**, Soliman OI, Vletter WB, ten Cate FJ, Geleijnse ML. Age-related changes in the biomechanics of left ventricular twist measured by speckle tracking echocardiography. *Am J Physiol Heart Circ Physiol* 2008; **295**: H1705-H1711 [PMID: 18723767]
19 **van Dalen BM**, Soliman OI, Kauer F, Vletter WB, Zwaan HB, Cate FJ, Geleijnse ML. Alterations in left ventricular untwisting with ageing. *Circ J* 2010; **74**: 101-108 [PMID: 19966501 DOI: 10.1253/circj.CJ-09-0436]
20 **Lumens J**, Delhaas T, Arts T, Cowan BR, Young AA. Impaired subendocardial contractile myofiber function in asymptomatic

aged humans, as detected using MRI. *Am J Physiol Heart Circ Physiol* 2006; **291**: H1573-H1579 [PMID: 16679404 DOI: 10.1152/ajpheart.00074.2006]

21 **Nikitin NP**, Witte KK, Thackray SD, de Silva R, Clark AL, Cleland JG. Longitudinal ventricular function: normal values of atrioventricular annular and myocardial velocities measured with quantitative two-dimensional color Doppler tissue imaging. *J Am Soc Echocardiogr* 2003; **16**: 906-921 [PMID: 12931102 DOI: 10.1016/S0894-7317(03)00279-7]

22 **Ashikaga H**, Criscione JC, Omens JH, Covell JW, Ingels NB. Transmural left ventricular mechanics underlying torsional recoil during relaxation. *Am J Physiol Heart Circ Physiol* 2004; **286**: H640-H647 [PMID: 14551052 DOI: 10.1152/ajpheart.00575.2003]

23 **Rademakers FE**, Buchalter MB, Rogers WJ, Zerhouni EA, Weisfeldt ML, Weiss JL, Shapiro EP. Dissociation between left ventricular untwisting and filling. Accentuation by catecholamines. *Circulation* 1992; **85**: 1572-1581 [PMID: 1555295 DOI: 10.1161/01.CIR.85.4.1572]

24 **Notomi Y**, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, Thomas JD. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 2008; **294**: H505-H513 [PMID: 18032523 DOI: 10.1152/ajpheart.00975.2007]

25 **van Dalen BM**, Soliman OI, Vletter WB, ten Cate FJ, Geleijnse ML. Insights into left ventricular function from the time course of regional and global rotation by speckle tracking echocardiography. *Echocardiography* 2009; **26**: 371-377 [PMID: 19054040]

26 **Kauer F**, van Dalen BM, Soliman OI, van der Zwaan HB, Vletter WB, Schinkel AF, ten Cate FJ, Geleijnse ML. Regional left ventricular rotation and back-rotation in patients with reverse septal curvature hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2013; **14**: 435-442 [PMID: 22898715]

27 **van Dalen BM**, Geleijnse ML. Left Ventricular Twist in Cardiomyopathy, Cardiomyopathies. Milei J, editor. InTech, 2013 [DOI: 10.5772/55281]

28 **Young AA**, Kramer CM, Ferrari VA, Axel L, Reichek N. Three-dimensional left ventricular deformation in hypertrophic cardiomyopathy. *Circulation* 1994; **90**: 854-867 [PMID: 8044957 DOI: 10.1161/01.CIR.90.2.854]

29 **van Dalen BM**, Kauer F, Soliman OI, Vletter WB, Michels M, ten Cate FJ, Geleijnse ML. Influence of the pattern of hypertrophy on left ventricular twist in hypertrophic cardiomyopathy. *Heart* 2009; **95**: 657-661 [PMID: 18977803]

30 **Cecchi F**, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med* 2003; **349**: 1027-1035 [PMID: 12968086 DOI: 10.1056/NEJMoa025050349/11/1027]

31 **Soliman OI**, Geleijnse ML, Michels M, Dijkmans PA, Nemes A, van Dalen BM, Vletter WB, Serruys PW, ten Cate FJ. Effect of successful alcohol septal ablation on microvascular function in patients with obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2008; **101**: 1321-1327 [PMID: 18435965]

32 **Takeuchi M**, Borden WB, Nakai H, Nishikage T, Kokumai M, Nagakura T, Otani S, Lang RM. Reduced and delayed untwisting of the left ventricle in patients with hypertension and left ventricular hypertrophy: a study using two-dimensional speckle tracking imaging. *Eur Heart J* 2007; **28**: 2756-2762 [PMID: 17951572 DOI: 10.1093/eurheartj/ehm440]

33 **van Dalen BM**, Kauer F, Michels M, Soliman OI, Vletter WB, van der Zwaan HB, ten Cate FJ, Geleijnse ML. Delayed left ventricular untwisting in hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2009; **22**: 1320-1326 [PMID: 19815387]

34 **van Dalen BM**, Tzikas A, Soliman OI, Heuvelman HJ, Vletter WB, Ten Cate FJ, Geleijnse ML. Assessment of subendocardial contractile function in aortic stenosis: a study using speckle tracking echocardiography. *Echocardiography* 2013; **30**: 293-300 [PMID: 23347129 DOI: 10.1111/echo.12051]

35 **van Dalen BM**, Tzikas A, Soliman OI, Kauer F, Heuvelman HJ, Vletter WB, ten Cate FJ, Geleijnse ML. Left ventricular twist and untwist in aortic stenosis. *Int J Cardiol* 2011; **148**: 319-324 [PMID: 20036018 DOI: 10.1016/j.ijcard.2009.11.022]

36 **Karaahmet T**, Gürel E, Tigen K, Güler A, Dündar C, Fotbolcu H, Basaran Y. The effect of myocardial fibrosis on left ventricular torsion and twist in patients with non-ischemic dilated cardiomyopathy. *Cardiol J* 2013; **20**: 276-286 [PMID: 23788302 DOI: 10.5603/CJ.2013.0073]

37 **van Dalen BM**, Soliman OI, Vletter WB, ten Cate FJ, Geleijnse ML. Left ventricular untwisting in restrictive and pseudorestrictive left ventricular filling: novel insights into diastology. *Echocardiography* 2010; **27**: 269-274 [PMID: 19765059]

38 **Kim HK**, Chang SA, Ahn HS, Shin DH, Kim JH, Lee SP, Kim YJ, Cho GY, Sohn DW, Oh BH, Park YB. Load independence of two-dimensional speckle-tracking-derived left ventricular twist and apex-to-base rotation delay in nonischemic dilated cardiomyopathy: implications for left ventricular dyssynchrony assessment. *J Am Soc Echocardiogr* 2012; **25**: 652-660 [PMID: 22465871 DOI: 10.1016/j.echo.2012.03.002]

39 **Ritter M**, Oechslin E, Sütsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. *Mayo Clin Proc* 1997; **72**: 26-31 [PMID: 9005281 DOI: 10.4065/72.1.26]

40 **Maron BJ**, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006; **113**: 1807-1816 [PMID: 16567565 DOI: 10.1161/CIRCULATIONAHA.106.174287]

41 **Sen-Chowdhry S**, McKenna WJ. Left ventricular noncompaction and cardiomyopathy: cause, contributor, or epiphenomenon? *Curr Opin Cardiol* 2008; **23**: 171-175 [PMID: 18382203 DOI: 10.1097/HCO.0b013e3282fdc939]

42 **Sanchez-Quintana D**, Garcia-Martinez V, Climent V, Hurle JM. Morphological changes in the normal pattern of ventricular myoarchitecture in the developing human heart. *Anat Rec* 1995; **243**: 483-495 [PMID: 8597295 DOI: 10.1002/ar.1092430411]

43 **Jenni R**, Oechslin EN, van der Loo B. Isolated ventricular non-compaction of the myocardium in adults. *Heart* 2007; **93**: 11-15 [PMID: 16670098 DOI: 10.1136/hrt.2005.082271]

44 **van Dalen BM**, Caliskan K, Soliman OI, Nemes A, Vletter WB, Ten Cate FJ, Geleijnse ML. Left ventricular solid body rotation in non-compaction cardiomyopathy: a potential new objective and quantitative functional diagnostic criterion? *Eur J Heart Fail* 2008; **10**: 1088-1093 [PMID: 18815069]

45 **Bellavia D**, Michelena HI, Martinez M, Pellikka PA, Bruce CJ, Connolly HM, Villarraga HR, Veress G, Oh JK, Miller FA. Speckle myocardial imaging modalities for early detection of myocardial impairment in isolated left ventricular non-compaction. *Heart* 2010; **96**: 440-447 [PMID: 19966109 DOI: 10.1136/hrt.2009.182170]

46 **Udink ten Cate FE**, Schmidt BE, Lagies R, Brockmeier K, Sreeram N. Reversed apical rotation and paradoxical increased left ventricular torsion in children with left ventricular non-compaction. *Int J Cardiol* 2010; **145**: 558-559 [PMID: 20920949 DOI: 10.1016/j.ijcard.2010.05.023]

47 **van Dalen BM**, Caliskan K, Soliman OI, Kauer F, van der Zwaan HB, Vletter WB, van Vark LC, Ten Cate FJ, Geleijnse ML. Diagnostic value of rigid body rotation in noncompaction cardiomyopathy. *J Am Soc Echocardiogr* 2011; **24**: 548-555 [PMID: 21345651]

48 **Peters F**, Khandheria BK, Libhaber E, Maharaj N, Dos Santos C, Matioda H, Essop MR. Left ventricular twist in left ventricular noncompaction. *Eur Heart J Cardiovasc Imaging* 2014; **15**: 48-55 [PMID: 23793875 DOI: 10.1093/ehjci/jet076]

49 **Nemes A**, Kalapos A, Domsik P, Forster T. Identification of left ventricular "rigid body rotation" by three-dimensional speckle-tracking echocardiography in a patient with noncompaction of the left ventricle: a case from the MAGYAR-Path Study. *Echocardiography* 2012; **29**: E237-E240 [PMID: 22748107 DOI: 10.1111/j.1540-8175.2012.01767.x]

50 **Rüssel IK**, Götte MJ. New insights in LV torsion for the selection of cardiac resynchronisation therapy candidates. *Neth Heart J* 2011; **19**: 386-391 [PMID: 21562790 DOI: 10.1007/s12471-011-0136-y]

51 **Nemes A**, Havasi K, Forster T. "Rigid body rotation" of the left ventricle in hypoplastic right-heart syndrome: a case from the three-dimensional speckle-tracking echocardiographic MAGYAR-Path Study. *Cardiol Young* 2015; **25**: 768-772 [PMID: 24932961 DOI: 10.1017/S1047951114000973]

52 **Kroeker CA**, Tyberg JV, Beyar R. Effects of ischemia on left ventricular apex rotation. An experimental study in anesthetized dogs. *Circulation* 1995; **92**: 3539-3548 [PMID: 8521577 DOI: 10.1161/01.CIR.92.1.130]

53 **Moen CA**, Salminen PR, Grong K, Matre K. Left ventricular strain, rotation, and torsion as markers of acute myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2011; **300**: H2142-H2154 [PMID: 21441314 DOI: 10.1152/ajpheart.01012.2010]

54 **Sun JP**, Niu J, Chou D, Chuang HH, Wang K, Drinko J, Borowski A, Stewart WJ, Thomas JD. Alterations of regional myocardial function in a swine model of myocardial infarction assessed by echocardiographic 2-dimensional strain imaging. *J Am Soc Echocardiogr* 2007; **20**: 498-504 [PMID: 17484990 DOI: 10.1016/j.echo.2006.10.029]

55 **Bansal M**, Leano RL, Marwick TH. Clinical assessment of left ventricular systolic torsion: effects of myocardial infarction and ischemia. *J Am Soc Echocardiogr* 2008; **21**: 887-894 [PMID: 18325731 DOI: 10.1016/j.echo.2008.01.011]

56 **Takeuchi M**, Nishikage T, Nakai H, Kokumai M, Otani S, Lang RM. The assessment of left ventricular twist in anterior wall myocardial infarction using two-dimensional speckle tracking imaging. *J Am Soc Echocardiogr* 2007; **20**: 36-44 [PMID: 17218200]

57 **Nagel E**, Stuber M, Lakatos M, Scheidegger MB, Boesiger P, Hess OM. Cardiac rotation and relaxation after anterolateral myocardial infarction. *Coron Artery Dis* 2000; **11**: 261-267 [PMID: 10832560 DOI: 10.1097/00019501-200005000-00009]

58 **Cirillo M**, Arpesella G. Rewind the heart: a novel technique to reset heart fibers' orientation in surgery for ischemic cardiomyopathy. *Med Hypotheses* 2008; **70**: 848-854 [PMID: 17935899 DOI: 10.1016/j.mehy.2007.07.047]

59 **Setser RM**, Smedira NG, Lieber ML, Sabo ED, White RD. Left ventricular torsional mechanics after left ventricular reconstruction surgery for ischemic cardiomyopathy. *J Thorac Cardiovasc Surg* 2007; **134**: 888-896 [PMID: 17903502 DOI: 10.1016/j.jtcvs.2007.05.060]

60 **Cirillo M**, Campana M, Brunelli F, Tomba MD, Mhagna Z, Messina A, Villa E, Troise G. 'Let's twist again': surgically induced renewal of left ventricular torsion in ischemic cardiomyopathy. *J Cardiovasc Med* (Hagerstown) 2010; **11**: 34-39 [PMID: 19834328 DOI: 10.2459/JCM.0b013e3283314483]

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MINIREVIEWS

Clinical significance of lactate in acute cardiac patients

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Abstract

Lactate, as a metabolite of easy and quick assessment, has been studied over time in critically ill patients in order to evaluate its prognostic ability. The present review is focused on the prognostic role of lactate levels in acute cardiac patients (that is with acute coronary syndrome, cardiogenic shock, cardiac arrest, non including post cardiac surgery patients). In patients with ST-elevation myocardial infarction treated with mechanical revascularization, hyperlactatemia identified a subset of patients at higher risk for early death and in-hospital complications, being strictly related mainly to hemodynamic derangement. The prognostic impact of hyperlactatemia on mortality has been documented in patients with cardiogenic shock and in those with cardiac arrest even if there is no cut-off value of lactate to be associated with worse outcome or to guide resuscitation or hemodynamic management. Therapeutic hypothermia seems to affect *per se* lactate values which have been shown to progressively decrease during hypothermia. The mechanism(s) accounting for lactate levels during hypothemia seem to be multiple ranging from the metabolic effects of reduced temperatures to the hemodynamic effects of hypothermia (*i.e.*, reduced need of vasopressor agents). Serial lactate measurements over time, or lactate clearance, have been reported to be clinically more reliable than lactate absolute value also in acute cardiac patients. Despite differences in study design, timing of lactate measurements and type of acute cardiac conditions (*i.e.*, cardiogenic shock, cardiac arrest, refractory cardiac arrest), available evidence strongly suggests that higher lactate levels can be observed on admission in non-survivors and that higher lactate clearance is associated with better outcome.

Key words: Lactate; Acute coronary syndrome; Cardiogenic shock; Cardiac arrest; Therapeutic hypothermia; Extracorporeal membrane oxygenation; Prognosis

Core tip: The present review is focused on the prognostic role of lactate levels in acute cardiac patients (acute coronary syndrome, cardiogenic shock, cardiac arrest). The prognostic impact of hyperlactatemia on mortality has been documented in cardiogenic shock and cardiac arrest even if there is no cut-off value of

lactate to be associated with worse outcome or to guide resuscitation or hemodynamic management. Lactate clearance was reported to be clinically more reliable than lactate absolute value in these patients. Despite differences in study design, timing of lactate measurements and type of acute cardiac conditions (*i.e.*, cardiogenic shock, cardiac arrest, refractory cardiac arrest), available evidence strongly suggests that higher lactate levels can be observed on admission in non-survivors and that a more favorable outcome is observed in patients with higher lactate clearance.

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INTRODUCTION

Hyperlactatemia is known to be associated with adverse outcome in critical illness[1-3]. However, the source, patho-physiology and metabolic function of lactate remain unclear probably because lactate is widely produced and it is cardinal to many energy-related pathways[4].

In recent years, available evidence strongly suggests that stress hyperlactatemia is due to increased aerobic lactate production with or without lactate clearance and that it is probably due to adrenergic stimulation. In other words, increased lactate levels are indicative of a stress response and lactate is a source of energy and not a waste product.

Lactate, since it is easy and quick to measure even at the bedside, has been widely investigated in critically ill patients to assess its prognostic role[5].

The present review is focused on the prognostic role of lactate levels in acute cardiac patients (acute coronary syndrome, cardiogenic shock, cardiac arrest). Post cardiac surgery patients are not included.

LACTATE IN THE HEART

In a normal heart, at rest, β-oxidation of fatty acids provides about 60%-90% of Adenosine triphosphate (ATP) while pyruvate produces 10%-40% of ATP[6]. However, fatty acids show lower production efficiency and increased intracellular free fatty acids activate uncoupling proteins, so that protones leak into the mitocondria without generating ATP[7]. That is why inhibition of β-oxidation is associated to an increased in mechanical efficiency of the left ventricle.

Lactate is an important fuel for the stressed heart[8]. During exercise the uptake of lactate by the myocardium and its use increase as well as during β-adrenergic stimulation and shock[4,9].

In presence of increased lactate concentrations, lactate might represent up to 60% of cardiac oxidative substrate. During shock, lactate is the most important fuel for the heart. Indeed, in laboratory animals, lactate depletion is associated with shock and mortality[10,11] while lactate infusion increased cardiac performance in cardiogenic and septic shock[12].

Hyperlactatemia can be viewed as part of the stress response including increased metabolic rate, sympathetic nervous system activation, accelerated glycolysis and a modified bioenergetic supply. In animals with cardiogenic shock[13] and in patients with cardiogenic shock, a marked increment in glycolysis and gluconeogenesis associated with hyperlactatemia was described[14]. In healthy subjects and in cardiogenic shock[12], it was observed, using an infusion of labelled lactate, that 50% of this lactate was oxidized and 20% used for glucose synthesis, without differences between the two subgroups. All these data strongly suggest that lactate is a source of energy in stress conditions.

PROGNOSTIC SIGNIFICANCE OF LACTATE

Acute coronary syndrome

Few investigations assessed whether lactate values are a diagnostic tool in patients with chest pain. In 129 patients with chest pain[15], lactate values measured on arrival identified those chest pain patients with critical cardiac illness (*i.e.*, severe congestive heart failure) while lactate concentrations within the normal range had a high negative predictive value for diagnosis of acute myocardial infarction (AMI). In patients arriving at the emergency department for suspected AMI[16], lactate values on arrival were highly sensitive for the diagnosis of AMI, mainly in those patients with more than 2 h of chest pain. In 229 patients admitted to coronary care unit[17] admission lactate showed the greatest predictive power for shock development.

To date, the prognostic significance of lactate in acute coronary syndrome (ACS), that is unstable angina, no ST elevation myocardial infarction and ST elevation myocardial infarction (STEMI), has been investigated in observational, mainly single-center, studies[18,19].

In 1176 STEMI patients[20], hyperlactatemia measured at arrival in the catheterization laboratory was associated with worse outcome measures [increased 30-d mortality, larger enzymatic infarct size and increased use of intra-aortic balloon pump (IABP)]. Among non survivors with admission lactates $\geqslant$ 1.8 mmol/L, the fifty percent died within a day after percutaneous coronary intervention (PCI). Hypotension, higher heart rate, poor Thrombolysis in myocardial infarction-flow, diabetes and non-smoking were independently associated with hyperlactatemia. In 253 STEMI non-diabetic patients with STEMI[21], lactate, measured after PCI, was an independent predictor of mortality together with C-peptide and homeostatic model assessment, an index of acute insulin resistance.

In 807 STEMI patients treated with PCI[22], our group observed that lactate values were independently associated with early mortality only in the subgroup of patients in advanced Killip classes. Lactate concentrations (measured in the early phase of STEMI) were influenced by the degree of hemodynamic impairment (as indicated by Killip class), of myocardial ischemia (as inferred by Tn I), and by glucose values.

Moreover, lactate represented an independent marker for complications (acute pulmonary edema and arrhythmia) observed during intensive cardiac care unit (ICCU) stay in 445 STEMI patients[19] and in 481 ACS patients with cardiogenic shock treated with IABP, lactate was an independent predictor of IABP-related complications (hemorrhagic, ischemic events) together with use of inotropes and nadir platelet count[22].

Overall, according to the available evidence hyperlactatemia in STEMI patients submitted to primary PCI identified a subset of patients at higher risk for early death and in-hospital complications, being strictly related mainly to hemodynamic derangement. Similarly in 754 consecutive patients with acute decompensated heart failure (ADHF) (ACS in the 52%)[23] admission lactate values > 3.2 mmol/L were associated with increased in-hospital mortality in ADHF patients either with or without ACS.

Cardiogenic shock

In 2006, in 38 patients with cardiogenic shock (CS) following acute myocardial infarction and retrospectively analyzed, interleukin-6 concentrations were independently associated with increased 30-d mortality while lactate values were not[24]. In the following years, increasing evidence supported the notion of lactate as a prognostic factor in circulatory shock[14,25]. In 45 CS patients complicating STEMI[26], increased lactate values (that is > 6.5 mmol/L) were independently associated with in-hospital death. Similar results were reported in other investigations[27,28].

The strict relationship relation between lactate and hemodynamic impairment was documented in 25 CS patients in whom a short-term increase in mean arterial pressure with norepinephrine was associated with a significant reduction in lactate levels, better cardiac performance and improved microcirculatory variables[29].

So far there is no cut-off value of lactate associated with worse outcome[30]. Lactate values higher than 2.0 mmol per liter was one of the diagnostic criteria for impaired end-organ perfusion (together with altered mental status; cold, clammy skin and extremities; oliguria with urine output of less than 30 mL/h) in a randomized multicenter trial, including 600 CS patients complicating AMI randomized to intraaortic balloon counterpulsation (301 patients) or no intraaortic balloon counterpulsation (299 patients). Intra-aortic balloon pump did not affect serum lactate concentration as well as the length of ICU stay, catecholamine therapy (dose and duration), and renal function and its use was not associated with a reduced 30-d mortality.

Cardiac arrest

The prognostic significance of lactate levels in cardiac arrest was investigated mainly in observational studies, not homogeneous for study design, inclusion criteria (cardiac arrest of cardiac/not cardiac origin) and time and number of lactate determination. The influence on lactate value of treatments such as mild hypothermia and support therapy like extracorporeal membrane oxygenation (ECMO) are so far not completely elucidated. Thus, there is no cut-off of lactate values in post-cardiac arrest patients to be associated with increased mortality and/or neurological impairment or to be use to guide resuscitation or post-resuscitation hemodynamic management.

Hyperlactatemia observed in the early phase in cardiac arrest patients may be related to both the ischaemia that occurs during arrest and to the inflammation resulting from ischemia-reperfusion injury[31-34].

Hyperlactatemia in post cardiac patients has been reported in several investigations[31-34]. In 128 out-of-hospital cardiac arrest patients[33] it was reported a progressive increased mortality associated with hyperlactatemia (39% lactate < 5 mmol/L, 67% lactate 5 mmol/L to 10 mmol/L, and 92% lactate ⩾ 10 mmol/L; $P < 0.001$). In out-of-hospital cardiac arrest (OHCA) patients[35] blood ammonia and lactate on arrival were independent prognostic factors and, when combining both biomarkers, the positive predictive value was nearly 100%.

An association between lactate levels and neurological outcome has been documented in recent investigations[36]. In 930 cardiac arrest patients who underwent therapeutic hypothermia (TH) collected from the Korean Hypothermia Network[37] high levels of lactate measured 1 h after return of spontaneous circulation were related to early mortality and poor neurological outcome. In 184 OHCA patients[38], lactate levels < 5 mmol/L and lower epinephrine doses (< 1.5 mg) were predictors of a normal Glasgow Coma Scale. Lactate concentrations measured at 6, 12, 24 and 48 h were significantly lower in the good neurological outcome group than in the poor neurological outcome group, while admission lactate values were comparable between the two subgroups. Moreover, in 76 OHCA patients submitted to TH, lactate clearance (6-h and 12-h) was related to good neurological outcome also when adjusted for confounding factors[39].

However, data on the effect of therapeutic hypothermia on lactate values are so far not uniform. In a prospective trial comparing moderate induced hypothermia with normothermia in OHCA survivors[40], during hypothermia it was reported an increment in lactate values, together with reduced pH values, reduced MAP and increased glucose levels. On the other hand, when comparing therapeutic hypothermia and normothermia[41], no significant difference in peak lactate values, arterial pressure, and need of vasopressors was reported in comatose survivors of ventricular fibrillation with STEMI. On the other hand,

in 20 CS patients after successful resuscitation[42], the initially increased lactate levels were lower in the hypothermic than the control group.

When measured serially during hypothermia in cardiac arrest patients[43], the lactate levels decreased from induction (6.68 ± 3.64; 0.5-1.7 mmol/L) to the maintenance phase (3.29 ± 2.44) and normalized in the rewarming phase.

Recently[44], in 33 cardiac arrest patients treated with TH, we observed that lactate values showed a progressive reduction during hypothermia, reduction which was independent of blood pressure variations, since mean arterial pressure showed no significant changes throughout hypothermia and of volemia (central venous pressure remained unvaried). It can be hypothesized that in patients submitted to TH lactate values are influenced by more complex mechanism(s) beyond perfusion (as indicated by mean arterial pressure) and/or volemia (as inferred by central venous pressure). We can suppose that the metabolic effect(s) of temperature may have contributed to lactate reduction, since hypothermia induces a reduction in metabolic rate (8% per degree centigrade drop in core temperature)[45] and in oxygen consumption (as previously observed when applying therapeutic hypothermia to critically ill febrile patients)[46]. In addition, pharmacological agents may have affected lactate values, since vasoactive pharmacological drugs influences the rate of glycolysis, where the rate of pyruvate utilization does not meet the rate of glycolysis, leading to lactate production[47]. As a matter of fact, in cardiac arrest patients[44] a decrease in vasopressor dose was observed during hypothermia.

In our series, lactate levels when measured during hypotermia were associated with in-ICCU death and, similarly, in 199 post cardiac arrest patients submitted to hypothermia[48], lactate (at 12 and 24 h, respectively) were significantly associated with adverse outcomes.

In the last years, a few reports analyzed the relation between hyperlactatemia and mortality in patients with refractory cardiac arrest treated with venous-arterial ECMO support. In 57 patients with refractory cardiac arrest who received ECMO during cardiopulmonary resuscitation, recruited over a six-year period[49], lactate values (measured on the first, third and seventh days, respectively) showed a significant correlation with weaning and survival. In 66 CA patients treated with ECMO, lactate concentration ⩾ 21 mmol/L (measured before cannulation) was associated with worse outcome together with fibrinogen ⩽ 0.8 g/L, and prothrombin index ⩽ 11%[50]. More recently, in 15 consecutive OHCA patients due to acute coronary syndrome submitted ECMO support, combination of base excess (less than -10 mmol/L) and lactate (> 12 mmol/L), measured 3 h after starting ECMO, can be used to predict multiorgan failure occurrence and mortality in the following 21 h[51].

LACTATE CLEARANCE

Lactate clearance have been reported to be more reliable on clinical grounds than absolute value of lactate for risk stratification in different critically ill conditions, ranging from sepsis to trauma[52-59].

Lactate clearance in acute cardiac patients has been investigated to date in few reports, all including observational single-center investigations performed in different populations of acute cardiac patients. Despite differences in study design, timing of lactate measurements and type of acute cardiac conditions (*i.e.*, cardiogenic shock, cardiac arrest, refractory cardiac arrest), available evidence strongly suggests that higher lactate levels can be observed on admission in non-survivors and that higher lactate clearance is related to more favourable outcome.

In 394 survivors from cardiac arrest[60], serum lactate levels, measured on admission and at 48 h, was retrospectively analyzed. Lactate values were lower in survivors at 6-mo after cardiac arrest than in non-survivors.

In 51 CS patients complicating STEMI[61], we observed that a 12-h lactate clearance < 10% was independently associated with early death and with poor survival rate at follow up. Since a more compromised renal failure (as indicated by a lower estimated glomerular filtration rate) was observed in patients with a low lactate clearance, associated with a lack of differences in haemodynamics (left-ventricular ejection fraction and mean arterial pressure) and transaminase values (as indexes of liver function), we supposed that a more compromised renal function may have a role in the development of persistent hyperlactataemia in these patients. Since no differences were observed in mean arterial pressure, left ventricular ejection fraction, and incidence of PCI failure between patients with 12 lactate clearance < 10% and those with 12 lactate clearance ⩾ 10%, it cannot be ruled out that microvascular alterations (despite global hemodynamic restoration) may be responsible for persistent increased lactate values in patients who exhibited a 12 lactate clearance < 10%.

Similarly, in 96 CS patients following AMI treated with percutaneous cardiopulmonary support, lactate clearance calculated at 48 h < 70% was one of the independent predictors for in-hospital mortality[62] (together with older age ⩾ 67 years and unsuccessful revascularization).

Data on the lactate clearance in patients with cardiac arrest supported by ECMO are quite scarce and not uniform.

In a heterogeneous series of 43 patients supported by ECMO for cardiogenic shock or cardiac arrest, hyperlactatemia at 6 h after ECMO implantation were observed in patients who died within 30 d[63].

In 51 patients who hadwitnessed out-of-hospital refractory cardiac arrest and were supported by ECMO upon arrival in the hospital[64], lactate clearance (values were measured before and 1-2 h after ECMO implantation) was greater in patients who survived. Conversely, in 24 patients with refractory cardiac supported by ECMO[65] lactate values, measured on

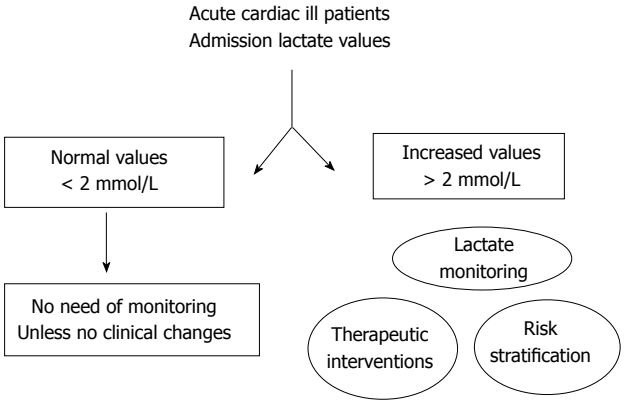

Figure 1 Admission lactate values.

admission, at 12 h and at 24 h, significantly decreased over time, with no differences between non-survivors and survivors and with no influence on outcome. A strict relation was documented between lactate and mean arterial (that is system perfusion) which increased both in survivors and in non-survivors. This relation probably explains why no difference was detectable in the dynamic behavior of lactate values during the first 24 h since admission between survivors and non survivors. Moreover, since lactate values can be related to mean arterial pressure (and not to renal function or gluycemia) it can be supposed that they may be considered a marker of perfusion, that is ECMO support efficacy in these patients.

CONCLUSION

In patients with acute coronary syndrome, cardiogenic shock and/or cardiac arrest, data on the prognostic impact of hyperlactatemia mainly stem from observational investigations. However, hyperlactatemia in these patients is associated with worse outcome, even if a cut-off value of lactate is so far not available.

Serial lactate measurements or lactate clearance have been reported to be more reliable for risk stratification in acute cardiac patients and, on a clinical ground, repeated measurement of lactate is highly advisable especially in those patients who showed increased values on admission (Figure 1). Further investigations are needed to identify the cut-off value of lactate to guide hemodynamic management.

REFERENCES

1 **Khosravani H**, Shahpori R, Stelfox HT, Kirkpatrick AW, Laupland KB. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. *Crit Care* 2009; **13**: R90 [PMID: 19523194 DOI: 10.1186/cc7918]
2 **Cerović O**, Golubović V, Spec-Marn A, Kremzar B, Vidmar G. Relationship between injury severity and lactate levels in severely injured patients. *Intensive Care Med* 2003; **29**: 1300-1305 [PMID: 12904861 DOI: 10.1007/s00134-003-1753-8]
3 **Nguyen HB**, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004; **32**: 1637-1642 [PMID: 15286537 DOI: 10.1097/01.CCM.0000132904.35713.A7]
4 **Garcia-Alvarez M**, Marik P, Bellomo R. Stress hyperlactataemia: present understanding and controversy. *Lancet Diabetes Endocrinol* 2014; **2**: 339-347 [PMID: 24703052 DOI: 10.1016/S2213-8587(13)70154-2]
5 **Attanà P**, Lazzeri C, Picariello C, Dini CS, Gensini GF, Valente S. Lactate and lactate clearance in acute cardiac care patients. *Eur Heart J Acute Cardiovasc Care* 2012; **1**: 115-121 [PMID: 24062898 DOI: 10.1177/2048872612451168]
6 **Beadle RM**, Frenneaux M. Modification of myocardial substrate utilisation: a new therapeutic paradigm in cardiovascular disease. *Heart* 2010; **96**: 824-830 [PMID: 20478861 DOI: 10.1136/hrt.2009.190256]
7 **Borst P**, Loos JA, ChrisT EJ, Slater EC. Uncoupling activity of long-chain fatty acids. *Biochim Biophys Acta* 1962; **62**: 509-518 [PMID: 13871487 DOI: 10.1016/0006-3002(62)90232-9]
8 **Hütter JF**, Schweickhardt C, Piper HM, Spieckermann PG. Inhibition of fatty acid oxidation and decrease of oxygen consumption of working rat heart by 4-bromocrotonic acid. *J Mol Cell Cardiol* 1984; **16**: 105-108 [PMID: 6699916 DOI: 10.1016/S0022-2828(84)80718-X]
9 **Lopaschuk GD**, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. *Physiol Rev* 2010; **90**: 207-258 [PMID: 20086077 DOI: 10.1152/physrev.00015.2009]
10 **Levy B**, Mansart A, Montemont C, Gibot S, Mallie JP, Regnault V, Lecompte T, Lacolley P. Myocardial lactate deprivation is associated with decreased cardiovascular performance, decreased myocardial energetics, and early death in endotoxic shock. *Intensive Care Med* 2007; **33**: 495-502 [PMID: 17242933]
11 **Barbee RW**, Kline JA, Watts JA. Depletion of lactate by dichloroacetate reduces cardiac efficiency after hemorrhagic shock. *Shock* 2000; **14**: 208-214 [PMID: 10947168 DOI: 10.1097/00024382-200014020-00022]
12 **Revelly JP**, Tappy L, Martinez A, Bollmann M, Cayeux MC, Berger MM, Chioléro RL. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. *Crit Care Med* 2005; **33**: 2235-2240 [PMID: 16215376 DOI: 10.1097/01.CCM.0000181525.99295.8F]
13 **Daniel AM**, Taylor ME, Kapadia B, MacLean LD. Metabolism of prolonged shock. *Adv Shock Res* 1983; **9**: 19-30 [PMID: 6880970]
14 **Chioléro RL**, Revelly JP, Leverve X, Gersbach P, Cayeux MC, Berger MM, Tappy L. Effects of cardiogenic shock on lactate and glucose metabolism after heart surgery. *Crit Care Med* 2000; **28**: 3784-3791 [PMID: 11153615 DOI: 10.1097/00003246-200012000-00002]
15 **Schmiechen NJ**, Han C, Milzman DP. ED use of rapid lactate to evaluate patients with acute chest pain. *Ann Emerg Med* 1997; **30**: 571-577 [PMID: 9360564 DOI: 10.1016/S0196-0644(97)70071-4]
16 **Gatien M**, Stiell I, Wielgosz A, Ooi D, Lee JS. Diagnostic performance of venous lactate on arrival at the emergency department for myocardial infarction. *Acad Emerg Med* 2005; **12**: 106-113 [PMID: 15692129 DOI: 10.1111/j.1553-2712.2005.tb00844.x]
17 **Mavrić Z**, Zaputović L, Zagar D, Matana A, Smokvina D. Usefulness of blood lactate as a predictor of shock development in acute myocardial infarction. *Am J Cardiol* 1991; **67**: 565-568 [PMID: 2000787 DOI: 10.1016/0002-9149(91)90892-O]
18 **Kossaify A**, Garcia A, Succar S, Ibrahim A, Moussallem N, Kossaify M, Grollier G. Perspectives on the value of biomarkers in acute cardiac care and implications for strategic management. *Biomark Insights* 2013; **8**: 115-126 [PMID: 24046510 DOI: 10.4137/BMI.S12703]
19 **Lazzeri C**, Valente S, Chiostri M, Picariello C, Gensini GF. Evaluation of acid-base balance in ST-elevation myocardial infarction in the early phase: a prognostic tool? *Coron Artery Dis* 2010; **21**: 266-272 [PMID: 20617567]
20 **Vermeulen RP**, Hoekstra M, Nijsten MW, van der Horst IC, van Pelt LJ, Jessurun GA, Jaarsma T, Zijlstra F, van den Heuvel AF. Clinical correlates of arterial lactate levels in patients with ST-segment elevation myocardial infarction at admission: a descriptive

study. *Crit Care* 2010; **14**: R164 [PMID: 20825687 DOI: 10.1186/cc9253]

21 **Lazzeri C**, Sori A, Chiostri M, Gensini GF, Valente S. Prognostic role of insulin resistance as assessed by homeostatic model assessment index in the acute phase of myocardial infarction in nondiabetic patients submitted to percutaneous coronary intervention. *Eur J Anaesthesiol* 2009; **26**: 856-862 [PMID: 19367169 DOI: 10.1097/EJA.0b013e32832a235c]

22 **Valente S**, Lazzeri C, Crudeli E, Chiostri M, Giglioli C, Bernardo P, Gensini GF. Intraaortic balloon pump: incidence and predictors of complications in the Florence registry. *Clin Cardiol* 2012; **35**: 200-204 [PMID: 22147681 DOI: 10.1002/clc.20975]

23 **Kawase T**, Toyofuku M, Higashihara T, Okubo Y, Takahashi L, Kagawa Y, Yamane K, Mito S, Tamekiyo H, Otsuka M, Okimoto T, Muraoka Y, Masaoka Y, Shiode N, Hayashi Y. Validation of lactate level as a predictor of early mortality in acute decompensated heart failure patients who entered intensive care unit. *J Cardiol* 2015; **65**: 164-170 [PMID: 24970716 DOI: 10.1016/j.jjcc.2014.05.006]

24 **Geppert A**, Dorninger A, Delle-Karth G, Zorn G, Heinz G, Huber K. Plasma concentrations of interleukin-6, organ failure, vasopressor support, and successful coronary revascularization in predicting 30-day mortality of patients with cardiogenic shock complicating acute myocardial infarction. *Crit Care Med* 2006; **34**: 2035-2042 [PMID: 16775569 DOI: 10.1097/01.CCM.0000228919.33620.D9]

25 **Weil MH**, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation* 1970; **41**: 989-1001 [PMID: 5482913 DOI: 10.1161/01.CIR.41.6.989]

26 **Valente S**, Lazzeri C, Vecchio S, Giglioli C, Margheri M, Bernardo P, Comeglio M, Chiocchini S, Gensini GF. Predictors of in-hospital mortality after percutaneous coronary intervention for cardiogenic shock. *Int J Cardiol* 2007; **114**: 176-182 [PMID: 16737749 DOI: 10.1016/j.ijcard.2006.01.024]

27 **Attanà P**, Lazzeri C, Chiostri M, Picariello C, Gensini GF, Valente S. Strong-ion gap approach in patients with cardiogenic shock following ST-elevation myocardial infarction. *Acute Card Care* 2013; **15**: 58-62 [PMID: 23806089 DOI: 10.3109/17482941.2013.776691]

28 **Koreny M**, Karth GD, Geppert A, Neunteufl T, Priglinger U, Heinz G, Siostrzonek P. Prognosis of patients who develop acute renal failure during the first 24 hours of cardiogenic shock after myocardial infarction. *Am J Med* 2002; **112**: 115-119 [PMID: 11835949]

29 **Perez P**, Kimmoun A, Blime V, Levy B. Increasing mean arterial pressure in cardiogenic shock secondary to myocardial infarction: effects on hemodynamics and tissue oxygenation. *Shock* 2014; **41**: 269-274 [PMID: 24509521 DOI: 10.1097/SHK.0000000000000099]

30 **Englehart MS**, Schreiber MA. Measurement of acid-base resuscitation endpoints: lactate, base deficit, bicarbonate or what? *Curr Opin Crit Care* 2006; **12**: 569-574 [PMID: 17077689 DOI: 10.1097/MCC.0b013e328010ba4f]

31 **Andersen LW**, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. *Mayo Clin Proc* 2013; **88**: 1127-1140 [PMID: 24079682 DOI: 10.1016/j.mayocp.2013.06.012]

32 **Donnino MW**, Miller J, Goyal N, Loomba M, Sankey SS, Dolcourt B, Sherwin R, Otero R, Wira C. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. *Resuscitation* 2007; **75**: 229-234 [PMID: 17583412 DOI: 10.1016/j.resuscitation.2007.03.021]

33 **Cocchi MN**, Miller J, Hunziker S, Carney E, Salciccioli J, Farris S, Joyce N, Zimetbaum P, Howell MD, Donnino MW. The association of lactate and vasopressor need for mortality prediction in survivors of cardiac arrest. *Minerva Anestesiol* 2011; **77**: 1063-1071 [PMID: 21597442]

34 **Nolan JP**, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT, Merchant RM, Morley P, Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Hoek TV. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation* 2008; **79**: 350-379 [PMID: 18963350 DOI: 10.1016/j.resuscitation.2008.09.017]

35 **Shinozaki K**, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Watanabe E, Tateishi Y, Nakanishi K, Kitamura N, Sato Y, Hirasawa H. Blood ammonia and lactate levels on hospital arrival as a predictive biomarker in patients with out-of-hospital cardiac arrest. *Resuscitation* 2011; **82**: 404-409 [PMID: 21227564 DOI: 10.1016/j.resuscitation.2010.10.026]

36 **Müllner M**, Sterz F, Domanovits H, Behringer W, Binder M, Laggner AN. The association between blood lactate concentration on admission, duration of cardiac arrest, and functional neurological recovery in patients resuscitated from ventricular fibrillation. *Intensive Care Med* 1997; **23**: 1138-1143 [PMID: 9434919]

37 **Lee DH**, Cho IS, Lee SH, Min YI, Min JH, Kim SH, Lee YH. Correlation between initial serum levels of lactate after return of spontaneous circulation and survival and neurological outcomes in patients who undergo therapeutic hypothermia after cardiac arrest. *Resuscitation* 2015; **88**: 143-149 [PMID: 25450570 DOI: 10.1016/j.resuscitation.2014.11.005]

38 **Kaji AH**, Hanif AM, Bosson N, Ostermayer D, Niemann JT. Predictors of neurologic outcome in patients resuscitated from out-of-hospital cardiac arrest using classification and regression tree analysis. *Am J Cardiol* 2014; **114**: 1024-1028 [PMID: 25118118 DOI: 10.1016/j.amjcard.2014.06.031]

39 **Lee TR**, Kang MJ, Cha WC, Shin TG, Sim MS, Jo IJ, Song KJ, Jeong YK, Cho JH. Better lactate clearance associated with good neurologic outcome in survivors who treated with therapeutic hypothermia after out-of-hospital cardiac arrest. *Crit Care* 2013; **17**: R260 [PMID: 24172276 DOI: 10.1186/cc13090]

40 **Bernard SA**, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346**: 557-563 [PMID: 11856794]

41 **Knafelj R**, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 2007; **74**: 227-234 [PMID: 17383070]

42 **Zobel C**, Adler C, Kranz A, Seck C, Pfister R, Hellmich M, Kochanek M, Reuter H. Mild therapeutic hypothermia in cardiogenic shock syndrome. *Crit Care Med* 2012; **40**: 1715-1723 [PMID: 22487996 DOI: 10.1097/CCM.0b013e318246b820]

43 **Bergman R**, Braber A, Adriaanse MA, van Vugt R, Tjan DH, van Zanten AR. Haemodynamic consequences of mild therapeutic hypothermia after cardiac arrest. *Eur J Anaesthesiol* 2010; **27**: 383-387 [PMID: 19858724 DOI: 10.1097/EJA.0b013e3283333a7d]

44 **Lazzeri C**, Gensini GF, Sori A, Bernardo P, Chiostri M, Tommasi E, Grossi F, Valente S. Dynamic behaviour of lactate values during mild hypothermia in patients with cardiac arrest. *Eur Heart J Acute Cardiovasc Care* 2014; **3**: 176-182 [PMID: 24337917 DOI: 10.1177/2048872613514014]

45 **Polderman KH**, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med* 2009; **37**: 1101-1120 [PMID: 19237924 DOI: 10.1097/CCM.0b013e3181962ad5]

46 **Manthous CA**, Hall JB, Olson D, Singh M, Chatila W, Pohlman A, Kushner R, Schmidt GA, Wood LD. Effect of cooling on oxygen consumption in febrile critically ill patients. *Am J Respir Crit Care Med* 1995; **151**: 10-14 [PMID: 7812538 DOI: 10.1164/ajrccm.151.1.7812538]

47 **Ensinger H**, Weichel T, Lindner KH, Grünert A, Georgieff M. Are the effects of noradrenaline, adrenaline and dopamine infusions on VO2 and metabolism transient? *Intensive Care Med* 1995; **21**: 50-56 [PMID: 7560474 DOI: 10.1007/BF02425154]

48 **Starodub R**, Abella BS, Grossestreuer AV, Shofer FS, Perman

SM, Leary M, Gaieski DF. Association of serum lactate and survival outcomes in patients undergoing therapeutic hypothermia after cardiac arrest. *Resuscitation* 2013; **84**: 1078-1082 [PMID: 23402966 DOI: 10.1016/j.resuscitation.2013.02.001]

49 **Chen YS**, Chao A, Yu HY, Ko WJ, Wu IH, Chen RJ, Huang SC, Lin FY, Wang SS. Analysis and results of prolonged resuscitation in cardiac arrest patients rescued by extracorporeal membrane oxygenation. *J Am Coll Cardiol* 2003; **41**: 197-203 [PMID: 12535808]

50 **Mégarbane B**, Deye N, Aout M, Malissin I, Résière D, Haouache H, Brun P, Haik W, Leprince P, Vicaut E, Baud FJ. Usefulness of routine laboratory parameters in the decision to treat refractory cardiac arrest with extracorporeal life support. *Resuscitation* 2011; **82**: 1154-1161 [PMID: 21641711 DOI: 10.1016/j.resuscitation.2011.05.007]

51 **Jouffroy R**, Lamhaut L, Guyard A, Phillipe P, Deluze T, Jaffry M, Dagron C, Bourgoin W, Orsini JP, An K, Jouven X, Spaulding C, Carli P. Base excess and lactate as prognostic indicators for patients treated by extra corporeal life support after out hospital cardiac arrest due to acute coronary syndrome. *Resuscitation* 2014; **85**: 1764-1768 [PMID: 25447431 DOI: 10.1016/j.resuscitation.2014.10.012]

52 **Bakker J**, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996; **171**: 221-226 [PMID: 8619454 DOI: 10.1016/S0002-9610(97)89552-9]

53 **Abramson D**, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. *J Trauma* 1993; **35**: 584-588; discussion 588-589 [PMID: 8411283 DOI: 10.1097/00005373-199310000-00014]

54 **Vincent JL**, Dufaye P, Berré J, Leeman M, Degaute JP, Kahn RJ. Serial lactate determinations during circulatory shock. *Crit Care Med* 1983; **11**: 449-451 [PMID: 6406145 DOI: 10.1097/00003246-198306000-00012]

55 **Meregalli A**, Oliveira RP, Friedman G. Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. *Crit Care* 2004; **8**: R60-R65 [PMID: 15025779 DOI: 10.1186/cc2423]

56 **Odom SR**, Howell MD, Silva GS, Nielsen VM, Gupta A, Shapiro NI, Talmor D. Lactate clearance as a predictor of mortality in trauma patients. *J Trauma Acute Care Surg* 2013; **74**: 999-1004 [PMID: 23511137 DOI: 10.1097/TA.0b013e3182858a3e]

57 **Lindsay AJ**, Xu M, Sessler DI, Blackstone EH, Bashour CA. Lactate clearance time and concentration linked to morbidity and death in cardiac surgical patients. *Ann Thorac Surg* 2013; **95**: 486-492 [PMID: 22959571 DOI: 10.1016/j.athoracsur.2012.07.020]

58 **Zhang Z**, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis*. *Crit Care Med* 2014; **42**: 2118-2125 [PMID: 24797375 DOI: 10.1097/CCM.0000000000000405]

59 **Fuller BM**, Dellinger RP. Lactate as a hemodynamic marker in the critically ill. *Curr Opin Crit Care* 2012; **18**: 267-272 [PMID: 22517402 DOI: 10.1097/MCC.0b013e3283532b8a]

60 **Kliegel A**, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, Laggner AN. Serial lactate determinations for prediction of outcome after cardiac arrest. *Medicine* (Baltimore) 2004; **83**: 274-279 [PMID: 15342971]

61 **Attaná P**, Lazzeri C, Chiostri M, Picariello C, Gensini GF, Valente S. Lactate clearance in cardiogenic shock following ST elevation myocardial infarction: a pilot study. *Acute Card Care* 2012; **14**: 20-26 [PMID: 22356569 DOI: 10.3109/17482941.2011.655293]

62 **Park TK**, Yang JH, Choi SH, Song YB, Hahn JY, Choi JH, Sung K, Lee YT, Gwon HC, Lee SH. Clinical outcomes of patients with acute myocardial infarction complicated by severe refractory cardiogenic shock assisted with percutaneous cardiopulmonary support. *Yonsei Med J* 2014; **55**: 920-927 [PMID: 24954319 DOI: 10.3349/ymj.2014.55.4.920]

63 **Guenther S**, Theiss HD, Fischer M, Sattler S, Peterss S, Born F, Pichlmaier M, Massberg S, Hagl C, Khaladj N. Percutaneous extracorporeal life support for patients in therapy refractory cardiogenic shock: initial results of an interdisciplinary team. *Interact Cardiovasc Thorac Surg* 2014; **18**: 283-291 [PMID: 24336784 DOI: 10.1093/icvts/ivt505]

64 **Le Guen M**, Nicolas-Robin A, Carreira S, Raux M, Leprince P, Riou B, Langeron O. Extracorporeal life support follow-ing out-of-hospital refractory cardiac arrest. *Crit Care* 2011; **15**: R29 [DOI: 10.1186/cc9976]

65 **Attanà P**, Lazzeri C, Chiostri M, Gensini GF, Valente S. Dynamic behavior of lactate values in venous-arterial extracorporeal membrane oxygenation for refractory cardiac arrest. *Resuscitation* 2013; **84**: e145-e146 [PMID: 24012603 DOI: 10.1016/j.resuscitation.2013.07.007]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Right ventricular septal pacing: Safety and efficacy in a long term follow up

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Abstract

AIM: To evaluate the safety and efficacy of the permanent high interventricular septal pacing in a long term follow up, as alternative to right ventricular apical pacing.

METHODS: We retrospectively evaluated: (1) 244 patients (74 ± 8 years; 169 men, 75 women) implanted with a single (132 pts) or dual chamber (112 pts) pacemaker (PM) with ventricular screw-in lead placed at the right ventricular high septal parahisian site (SEPTAL pacing); (2) 22 patients with permanent pacemaker and low percentage of pacing (< 20%) (NO pacing); (3) 33 patients with high percentage (> 80%) right ventricular apical pacing (RVA). All patients had a narrow spontaneous QRS (101 ± 14 ms). We evaluated New York Heart Association (NYHA) class, quality of life (QoL), 6 min walking test (6MWT) and left ventricular function (end-diastolic volume, LV-EDV; end-systolic volume, LV-ESV; ejection fraction, LV-EF) with 2D-echocardiography.

RESULTS: Pacing parameters were stable during

follow up (21 mo/patient). In SEPTAL pacing group we observed an improvement in NYHA class, QoL score and 6MWT. While LV-EDV didn't significantly increase (104 ± 40 mL *vs* 100 ± 37 mL; P = 0.35), LV-ESV slightly increased (55 ± 31 mL *vs* 49 ± 27 mL; P = 0.05) and LV-EF slightly decreased (49% ± 11% *vs* 53% ± 11%; P = 0.001) but never falling < 45%. In the RVA pacing control group we observed a worsening of NYHA class and an important reduction of LV-EF (from 56% ± 6% to 43% ± 9%, P < 0.0001).

CONCLUSION: Right ventricular permanent high septal pacing is safe and effective in a long term follow up evaluation; it could be a good alternative to the conventional RVA pacing in order to avoid its deleterious effects.

Key words: Right ventricular septal pacing; Parahisian pacing; Resynchronization therapy; Left ventricular cardiac function; Permanent cardiac pacing

Core tip: We evaluated the safety and efficacy of the permanent high interventricular septal pacing in a long term follow up, as alternative to right ventricular apical pacing. We retrospective evaluated 244 patients with a narrow QRS implanted with a single/dual chamber pacemaker with ventricular screw-in lead placed at the right ventricular high septal (parahisian) site. Contemporary we checked the clinical evolution of two control groups of patients: without ventricular stimulation and with conventional right ventricular apical stimulation. In a long term follow up we observed stability of pacing parameters and ejection fraction, and improvement in New York Heart Association class, quality of life and exercise tolerance.

Occhetta E, Quirino G, Baduena L, Nappo R, Cavallino C, Facchini E, Pistelli P, Magnani A, Bortnik M, Francalacci G, Dell'Era G, Plebani L, Marino P. Right ventricular septal pacing: Safety and efficacy in a long term follow up. *World J Cardiol* 2015; 7(8): 490-498 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i8/490.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i8.490

INTRODUCTION

The treatment of atrioventricular block or sinus node disease is represented by artificial pacemaker implant; usually the ventricular catheter is placed in right ventricular apical (RVA) position. This therapy proved efficacious in long term follow up, granting improvement in life expectancy and quality of life (QoL). However, similarly to the negative hemodynamic and clinical effects of spontaneous left bundle branch block, new data have emerged showing negative effects of the left bundle branch block-like activation determined by RVA pacing[1-5].

Several published studies[6-10] demonstrated that more than 40% of the heart beats are paced from the right ventricular apex, an increase in the incidence of atrial fibrillation, heart failure, hospitalizations and even death is observed. When ventricular pacing is necessary permanently or for long periods of time, sites for a more physiologic pacing should be identified to avoid he occurrence of ventricular desynchronization[11-13].

A better way to pace the heart in case of intraventricular conduction delay (especially left bundle branch block) is biventricular pacing: comparing to RVA pacing, it can improve left ventricular ejection fraction and volumes and reduce mitral regurgitation and sympathetic nervous system activity[14-17]. His bundle pacing may be considered as a reliable and effective method to prevent mechanical desynchronization when intraventricular conduction is preserved and QRS is narrow[18,19]. However, it requires adjuntive skills and may be more challenging and time-consuming; it is not always applicable and higher pacing thresholds have to be accepted[20]. The right ventricular septal pacing in the parahisian area, early penetrating the His-Purkinje conduction system, produces a more physiological ventricular activation, very similar to the one that is achieved with direct His bundle pacing[21].

We aimed to evaluate feasibility, safety and long-term clinical efficacy of permanent right ventricular septal pacing in the parahisian area, performed to obtain a shorter QRS duration than that resulting from conventional right ventricular apical pacing.

MATERIALS AND METHODS

Population

From January 2001 to December 2011, we evaluated 244 patients implanted with a single or dual-chamber pacemaker with the ventricular lead positioned in the high interventricular septum (parahisian site): "SEPTAL pacing" group.

The patients were implanted at the Cardiology Clinic of Azienda Ospedaliero-Universitaria (AOU) Maggiore della Carità in Novara (School of Medicine, Study University of Piemonte Orientale, Italy) (181 patients), at the Division of Cardiology of the Ospedale Civile in Ivrea, Italy (50 patients), and at the Division of Cardiology of the Ospedale SS. Annunziata in Cosenza, Italy (22 patients).

The mean age of patients was 74 ± 8 years; 169 patients were men (69%) and 75 patients were women (31%). Inclusion criteria were: (1) permanent VVIR pacing after AV node ablation for permanent atrial fibrillation with uncontrolled (high) ventricular rate, despite negative dromothropic therapy comprising digoxin, beta-blockers and diltiazem as monotherapy or associated (51 patients; 21%); (2) permanent VVIR pacing in permanent atrial fibrillation with impaired AV conduction and low ventricular frequency (81 patients; 33%); (3) permanent DDD(R) pacemaker in patients

Table 1 Comparison of pre-implantation clinical features in the patient control groups (NO pacing and right ventricular apical pacing) and parahisian pacing group

	NO pacing	RVA pacing	PH pacing
Total patients	22 patients	33 patients	244 patients
Age (yr)	75 ± 7	77 ± 9	74 ± 8
Sex	13 M/9 F	21 M/12 F	169 M/ 75 F
NYHA class	1.09 ± 0.29	1.15 ± 0.36	2.13 ± 0.46
LV ejection fraction (%)	57 ± 5	55 ± 8	53 ± 11
LV end-dyastolic volume (cc)	89 ± 25	98 ± 22	100 ± 37
LV end-systolic volume (cc)	38 ± 13	47 ± 17	49 ± 27
Associated heart diseases	Ischemic heart disease: 6/22 (27%) Valvular heart disease: 2/22 (9%) Hypertensive heart disease: 2/22 (9%) No significant heart disease: 12/22 (55%)	Ischemic heart disease: 12/33 (37%) Valvular heart disease: 4/33 (12%) Hypertensive heart disease: 3/33 (9%) No significant heart disease: 14/33 (42%)	Ischemic heart disease: 80/244 (33%) Valvular heart disease: 29/244 (12%) Hypertensive heart disease: 90/244 (37%) No significant heart disease: 45/244 (18%)
Atrial fibrillation	1 (5%)	4 (12%)	132 (54%)
Sinus rhythm	21 (95%)	29 (88%)	112 (46%)

Comparison of pre-implantation clinical features in the patient control groups [NO pacing and right ventricular apical (RVA) pacing] and parahisian (PH) pacing group. NYHA: New York Heart Association; LV: Left ventricular.

with sinus rhythm and first and second degree AV block, symptomatic for syncope/dizziness (82 patients; 34%); and (4) permanent DDD(R) pacemaker in patients with sinus rhythm and complete AV block (30 patients; 12%).

All patients had a narrow spontaneous QRS complex (mean 101 ± 14 ms; always < 120 ms), detected at standard ECG; in patients with AV node ablation a narrow QRS was detected during junctional escape rhythm after radiofrequency (RF) AV ablation; in patients with atrial fibrillation not undergoing AV ablation, a narrow QRS was documented during 24-h Holter recording.

At the same time, we retrospectively evaluated two other "control groups" of patients (all implanted at the Cardiology Clinic of AOU Maggiore della Carità in Novara, School of Medicine, Study University of Piemonte Orientale, Italy): (1) 22 consecutive patients with ventricular apical pacing (single or dual chamber pacemakers) but percentage of permanent pacing < 20%, retrospectively detected by pacemaker telemetry, owing to the presence of spontaneous AV conduction and preserved intraventricular conduction (QRS < 120 ms): "NO pacing" control group; (2) 33 consecutive patients with a ventricular or dual-chamber pacemaker providing a high percentage of ventricular pacing (> 80%) in the apex of the right ventricle, always retrospectively detected by pacemaker memories: "RVA pacing" group.

Before the implantation procedure, all patients were planned to undergo a complete evaluation.

Following assessments were performed: (1) New York Heart Association (NYHA) functional class; (2) quality of life (QoL), evaluated with "Minnesota Living with Heart Failure" questionnaire[22]; (3) twenty-four hour Holter monitoring; (4) six-minute walking test; (5) standard 2D-echocardiogram with measurement of left ventricular end-diastolic (LV-EDV) and end-systolic (LV-ESV) volumes computed according to a biplane Simpson's method, and left ventricular ejection fraction (LV-EF).

Clinical characteristics of the population are presented in Table 1: enrolled patients presented LV-EF values close to the lower limit of the normal range, narrow QRS with normal electrical axis and moderate compromission of functional class.

Implant procedure

In patients with permanent atrial fibrillation and AV node ablation, pacing leads were placed after RF ablation procedure. A quadripolar RF catheter was used to map the His bundle and an active fixation bipolar lead was placed as near as possible to the hisian dipole of the catheter. A second conventional bipolar lead was placed at the right ventricular apex. The septal and the apical leads were then connected to the "atrial" and "ventricular" pacemaker channels, respectively. The pacemaker was programmed in "DDDR" mode with "short" atrio-ventricular delay (*i.e.*, 90 ms). Thus, if the parahisian stimulation was effective through the "atrial" channel, the following RVA pulse pacing was inhibited or delivered during the refractory period through the "ventricular" channel. While, in case of ineffective parahisian stimulation, the RVA pulse pacing ensured ventricular capture.

In patients with permanent atrial fibrillation and bradyarrhythmia (without indication to AV node ablation), a single chamber VVIR pacemaker was used and connected to the lead positioned in the parahisian area, without RVA back up lead.

In patients with sinus rhythm and advanced spontaneous AV block (first, second or third degree) a conventional atrial lead was placed in addition to the parahisian lead; both leads were connected to a DDD/

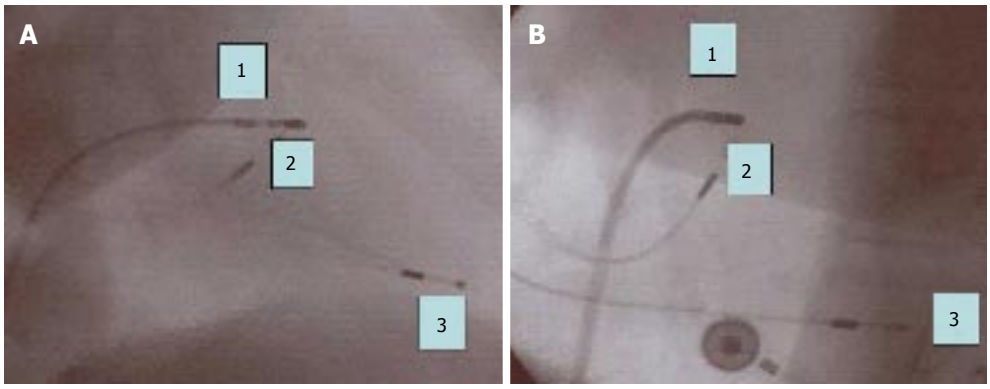

Figure 1 Antero-posterior (A) and left anterior oblique (B) fluoroscopic projections showing leads position after the "ablate and pace" procedure and parahisian pacing. 1 = quadripolar radiofrequency catheter mapping the Hisian site; 2 = screw-in bipolar lead positioned near the His-bundle; 3 = bipolar lead positioned in right ventricular apex.

DDDR pacemaker.

Following criteria were applied to obtain parahisian pacing[20]: (1) positioning of the tip of the screw-in lead as close as possible to the mapping dipole of the electrophysiological catheter (distance < 1 cm in left and right oblique projections) (Figure 1); (2) even if larger than the spontaneous QRS, the duration of the paced QRS had to be < 130 ms; (3) full concordance between electrical axis of the paced QRS and that of the spontaneous QRS; and (4) the pacing threshold had to be < 1 V (pacing of the muscular portion of the interventricular septum).

Control groups patients were implanted with a conventional apical right ventricular lead (and conventional atrial lead in dual chamber pacing).

Statistical analysis

Continuous variables with normal or Gaussian distribution of each group of patients were expressed in terms of average ± SD. Pre-implantation and follow-up data in the parahisian pacing group were analyzed and compared by means of the parametric Student *t* test for paired data. Similar parameters observed in the three groups were compared by means of the Student *t* test for numerically different samples with the same variance. A value of $P \leqslant 0.05$ was considered statistically significant.

The study was reviewed by our expert Biostatistic Gabriele Dell'Era, MD.

RESULTS

Implant data

To obtain the parahisian high septal pacing we used: (1) a bipolar catheter with 1.5 mm retractable screw lead (CapsureFix 4068/5068/5076; Medtronic Inc., Minneapolis, Minnesota) in 172 patients; (2) a bipolar catheter with 1.5 mm retractable screw lead (Cristalline ICQ09B, Vitatron BV, The Netherlands) in 10 patients; (3) a bipolar catheter with 1.5 mm retractable screw lead (Tendril 1488T/1888T; St.Jude Medical, Inc. St. Paul, Minnesota) in 12 patients; (4) a bipolar catheter with 3 mm retractable screw lead (10627 Medtronic Inc., Minneapolis, Minnesota) in 5 patients (controlled clinical evaluation); and (5) a bipolar, fixed screw, steroid eluting lead (Select Secure 3830, Medtronic Inc., Minneapolis, Minnesota) in 45 patients.

The total radiological exposure time was 15 ± 9 min (range from 3 to 68 min for the first implant with Select Secure system). Electrical parameters at the parahisian site were measured in bipolar configuration.

We excluded from the analysis 14 patients (6%), in which the criteria for parahisian pacing were not met, specifically the paced QRS was > 130 ms.

For patients in analysis, the average duration of the basal QRS was 101 ± 14 ms, and 122 ± 9 ms during parahisian pacing.

We obtained an average parahisian pacing threshold of 0.6 ± 0.3 V (at 0.5 ms pulse duration), pacing impedance 736 ± 238 Ω, endocavitary potential 10.1 ± 5.3 mV; we never recorded high-amplitude "far-field" type atrial potentials from the parahisian lead.

Parahisian pacing follow up

The average follow up of the 230 patients in analysis was 21 mo/patient, with a maximum of 70 mo for the first enrolled patient and a minimum of 12 mo for the last one.

In one patient a 3 cm dislodgment of the parahisian lead was reported. However, the paced QRS appeared superimposable to that recorded at the end of the implantation.

During long-term follow-up, the duration of the QRS during parahisian pacing remained comparable to that recorded at the implantation. Electrical measurements from the parahisian position remained stable and acceptable during time: pacing threshold was 0.6 ± 0.3 V at implantation and 0.8 ± 0.5 V at follow-up, mean endocardial potential was 10.1 ± 5.3 mV at implantation and 9.1 ± 4.4 mV at follow up, pacing impedance was 736 ± 238 ohms at implantationand 540 ± 116 ohms at follow up.

The clinical results at long-term follow-up were (Table 2): (1) In 167/230 patients (73%) we compared

Table 2 Long term follow up results of parahisian pacing

	Basal	Parahisian pacing	*P* value
NYHA class (167 pts)	2.15 ± 0.51	1.59 ± 0.55	< 0.001
6-min walk (m) (70 pts)	354 ± 90	400 ± 88	0.03
QoL (score) (70 pts)	29 ± 18	19 ± 7	0.02
LV-EDV (mL) (121 pts)	100 ± 37	104 ± 40	0.35
LV-ESV (mL) (121 pts)	49 ± 27	55 ± 31	0.05
LV-EF (%) (121 pts)	53 ± 11	49 ± 11	0.01

NYHA: New York Heart Association; QoL: Quality of life; LV-EDV: Left ventricular end diastolic volume; LV-ESV: Left ventricular end systolic volume; LV-EF: Left ventricular ejection fraction.

Table 3 New York Heart Association functional class before implantation and at follow-up, in patients with a low percentage of stimulation (NO pacing), with apical pacing (right ventricular apical pacing) and with parahisian pacing groups

	NO pacing (22 pts)	RVA pacing (33 pts)	PH pacing (167 pts)
Baseline	1.09 ± 0.29	1.15 ± 0.36	2.15 ± 0.51
Follow-up	1.22 ± 0.52	1.88 ± 0.99	1.59 ± 0.55
Significance	0.32 (ns)	*P* < 0.05	*P* < 0.001
	Unchanged	Worsening	Improvement

RVA: Right ventricular apical; PH: Para hisian.

NYHA functional class measured before implantation and at a mean follow-up of 18 ± 16 mo: the prolonged parahisian pacing led to a significant improvement from 2.15 ± 0.51 to 1.59 ± 0.55; $P < 0.001$ (Figure 2); (2) The quality of life score and exercise performances (6 min walk), performed in a sub-group of 70/230 patients (30%), significantly changed after a mean follow up of 14 ± 2 mo (QoL score from 29 ± 18 to 19 ± 17, $P = 0.02$; 6 min walk distance from 354 ± 90 m to 400 ± 88 m, $P = 0.03$) (Figure 2); (3) In 121/230 patients (53%) we compared echocardiographic volumes and ejection fraction before and after parahisian pacing (Figure 3): LV-EDV went from 100 ± 37 to 104 ± 40 mL, $P = 0.35$; LV-ESV from 49 ± 27 to 55 ± 31 mL, $P = 0.05$; LV-EF from 53% ± 11% to 49% ± 11%, $P = 0.01$. Medium-long term evaluation of the LV-EF showed values superimposable to enrollment values, confirming that parahisian pacing can prevent deterioration of the left ventricular function.

Control groups comparation

In RVA-paced patients QRS duration increased significantly (average 165 ± 10 ms, with values always > 130 ms).

In the "NO pacing" control group, the NYHA functional class was good both at the baseline and during follow-up; the conduction system disease did not significantly affect the functional class, which did not change during follow-up in the absence of ventricular pacing. By contrast, in "RVA pacing" patients there was a trend toward worsening NYHA functional class, though the upper classes of overt heart failure were not reached. Thus, during follow-up the NYHA functional class was better in patients without stimulation and those on PH stimulation (no significant difference between these two groups) and worse in patients stimulated at the apex ($P < 0.05$ *vs* unstimulated patients and *vs* PH-stimulated patients) (Table 3). QoL scores did not significantly differ among the three groups: 21 ± 19 score in NO pacing patients; 29 ± 13

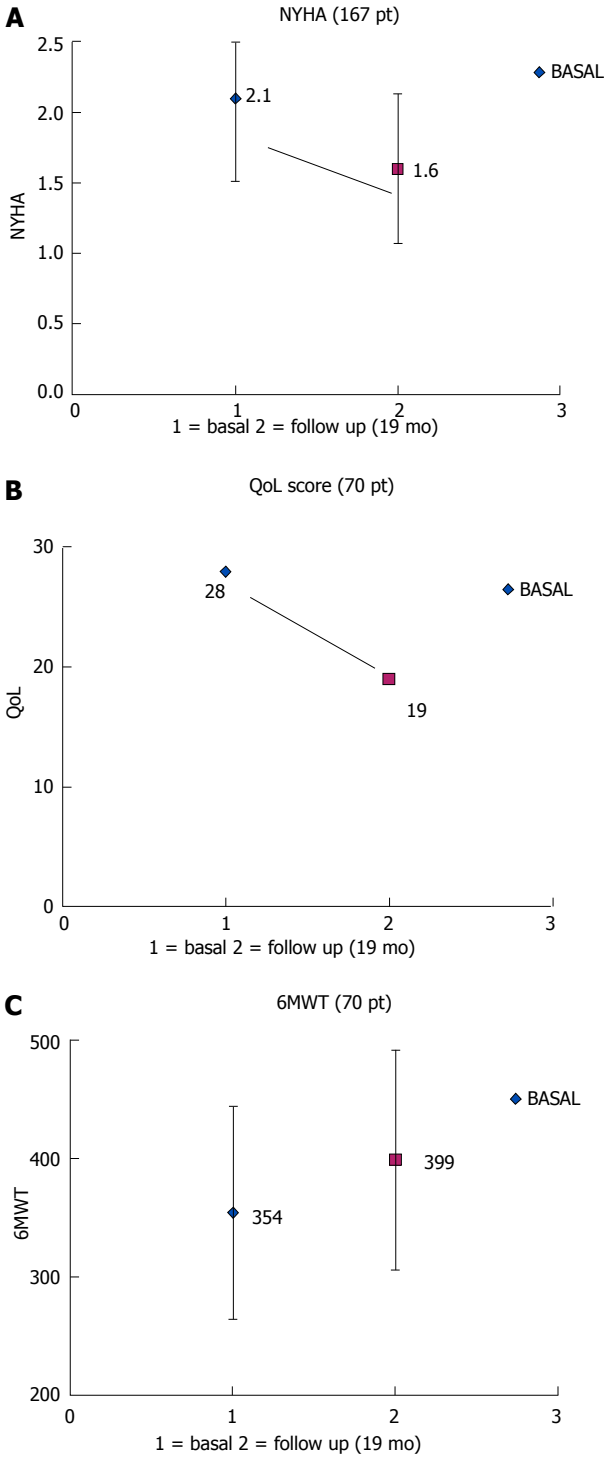

Figure 2 Clinical data before pacemaker implant (basal) and after septal pacing follow up. A: New York Heart Association functional class (NYHA); B: Quality of life (QoL) minnesota score; C: Six-minute walking test (6mwt) (meters).

Table 4 Evolution of echocardiographic parameters: end-diastolic volume, end-systolic volume and ejection fraction in the NO pacing group (22/22 patients), in the right ventricular apical pacing group (33/33 patients) and in the parahisian group (121/230 patients)

		Basal	Follow-up	*P*
Contr	EDV (mL)	88 ± 25	99 ± 46	0.23 (ns)
(22 pts)	ESV (mL)	38 ± 13	46 ± 29	0.11 (ns)
	EF (%)	57 ± 5	56 ± 5	0.1 (ns)
RVA	EDV (mL)	98 ± 23	139 ± 31	< 0.0001
(33 pts)	ESV (mL)	44 ± 14	79 ± 22	< 0.0001
	EF (%)	56 ± 6	43 ± 9	< 0.0001
PH	EDV (mL)	100 ± 37	104 ± 40	0.35 (ns)
(121 pts)	ESV (mL)	49 ± 27	55 ± 31	0.05
	EF (%)	53 ± 11	49 ± 11	0.01

in RVA pacing patients; 19 ± 17 in PH pacing patients (P < 0.06 RVA group *vs* NO pacing; P < 0.07 PH group *vs* NO pacing). Exercise tolerance, expressed in meters walked in 6 min, was better in patients without persistent pacing (448 ± 110 m) than in PH-stimulated patients (400 ± 88 m), but the difference was not significant; on the contrary it was worse in RVA-stimulated patients (338 ± 158 m) (P < 0.05 *vs* both "NO pacing" and PH-stimulated patients).

Left ventricular volumes and ejection fraction (EF) values in the controls and parahisian pacing groups of patients are shown in Table 4. In patients without significant ventricular pacing (NO pacing group), left ventricular function was almost unchanged during follow-up; indeed, no significant changes in volumes and EF were recorded (P = ns). All patients on ventricular pacing, however, presented some differences. The average end-diastolic and end-systolic volumes increased markedly in the RVA group, while in the PH group these volume increments were so modest as to be almost comparable to those observed in control patients. In RVA-paced patients, the increased left ventricular volumes led to a significant reduction in the mean EF to below normal values (post-pacing average of 43% ± 9% *vs* 56% ± 6% at the baseline; mean decrease of 13.2 percentage points, P < 0.0001); in PH patients, left ventricular function was fairly well preserved (post-pacing EF 49% ± 11%, *vs* 53% ± 11% baseline; mean change of 4 percentage points) (Figure 4).

DISCUSSION

Cardiac pacing aims at providing an adequate cardiac rhythm, restoring a physiological excito-conduction of the heart. Two elements are traditionally considered as cornerstone for "physiologic pacing": the maineinance of a correct atrioventricular sequence and the presence of chronotropic response (*via* rate-responsive sensors) during exercise or stress; till recent times, dual-chamber rate-response pacemakers were considered "physiological".

However, we know that conventional RVA pacing has the potential to induce electro-mechanichal desynchronization, causing potential harm (negative remodeling and worsening heart failure) in less than normal heart[23,24].

Therefore, a real physiological pacing must: (1) increase the cardiac frequency according to the metabolic needs; (2) keep correct atrioventricular sequence of activation; and (3) keep inter and intraventricular synchrony.

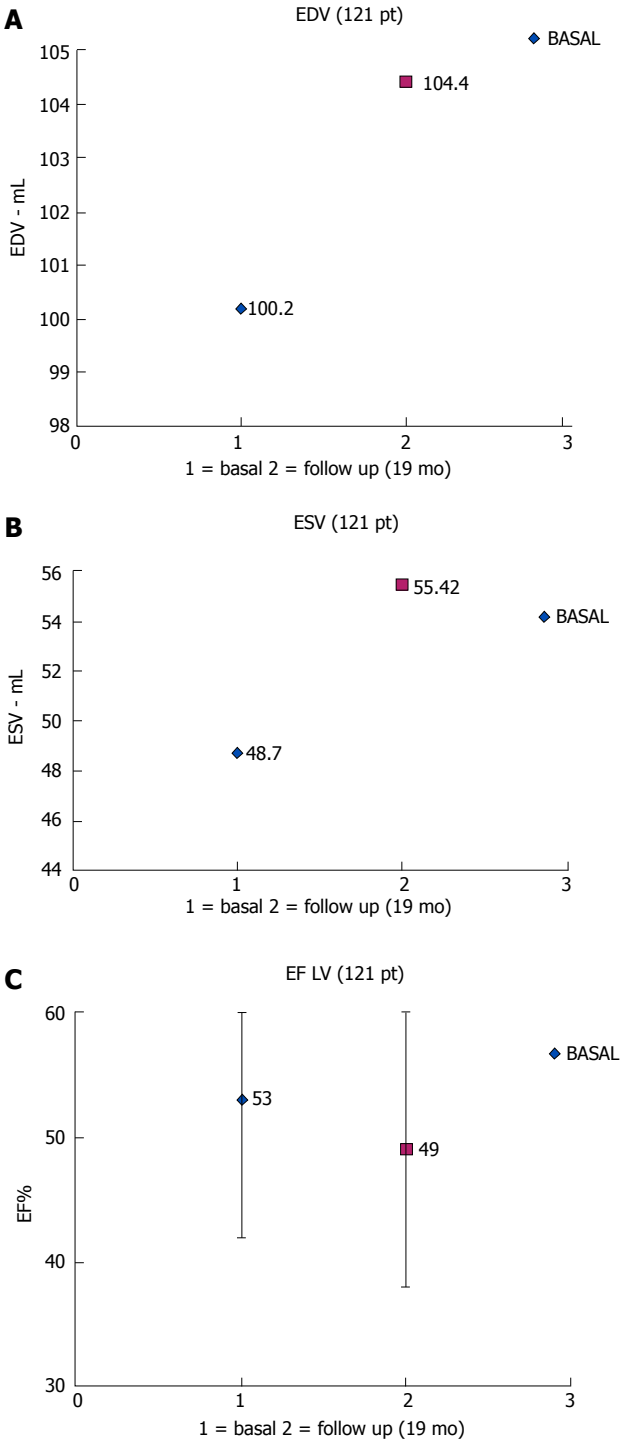

Figure 3 Echocardiographic data before pacemaker implant (basal) and after septal pacing follow up. A: End diastolic left ventricular volumes (EDV); B: End systolic left ventricular volumes (EDV); C: Left ventricular ejection fraction (EF LV).

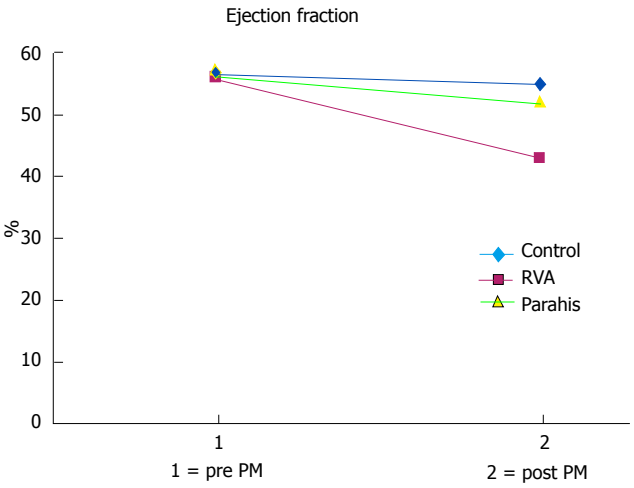

Figure 4 Average values of left ventricular ejection fraction at the baseline (1) and after two years of follow-up (2) in patients without significant stimulation (blue: control NO pacing), right ventricular apex paced patients (red: right ventricular apical) and parahisian paced patients (green: parahis). In control patients and PH patients, the ejection fraction remained essentially normal (values above 50%), while in RVA patients it declined significantly to average values of around 40. RVA: Right ventricular; PH: Parahisian.

Biventricular pacing proved effective in improving quality of life and cardiac function in patients with left bundle branch block (spontaneous electromechanical desynchronization)[14,17]. However, when intraventricular conduction is preserved and an atrioventricular block occurs, pacing must be as physiological as possible[25]. His bundle pacing has already established itself as an effective alternative to biventricular pacing for these patients. Indeed, it uses the His-Purkinje system without inducing intraventricular conduction delays[18,19]. Unfortunately, direct His bundle pacing may be challenging, needs high pacing electrical output and may pose the risk of traumatic (post-screwing of the pacing lead) His bundle block[20].

In our experience, a simpler and reliable method to achieve physiological intraventricular conduction is the so-called parahisian pacing: placing the tip of the catheter in the upper muscular part of the interventricular septum, activation is granted through the myocardium, but the His-Purkinje conduction system is activated at the same time[21]. With this technique, a fairly narrow (120-130 ms) QRS with an electrical axis concordant to the non-paced QRS can be obtained[26].

We already presented data about the improvement of hemodynamic and functional parameters obtained with parahisian pacing compared to conventional right apical pacing at a short follow up in patients undergoing AV node ablation for permanent atrial fibrillation with unsatisfactory rate control despite optimal therapy[27,28].

Long-term follow-up confirms these results, showing that parahisian pacing confers a durable improvement of quality of life, functional class and exercise tolerance. The improvement is sustained over time, modifying the expected natural progression of the underlying cardiopathy by means of a preserved atrioventricular and interventricular synchrony and by rate regularization; ejection fraction was positively affected, too, avoiding deterioration usually observed in paced patients.

Therefore, parahisian pacing should be considered easy to apply, reliable and effective in preventing the detrimental remodeling caused by non-physiological right ventricular apical pacing[29]. This kind of physiological pacing may be proposed as first line in patients needing high ventricular pacing percentage, presenting with preserved intraventricular conduction and mild systolic left ventricular dysfunction[30-32].

Limits of the study

The aim of the study was to evaluate the long term safety of septal parahisian permanent cardiac pacing and this has been definitively confirmed.

As for the long term efficacy of this pacing site, the main limitation of the study was the heterogeneity of our population: 54% of patients had atrial fibrillation (21% with concomitant AV node ablation) and VVIR pacing, 46% were in sinus rhythm with various AV block degrees and DDD(R) pacing.

This can surely affect the general prognosis, but all patients had an high percentage of ventricular pacing and a more "physiological" site of stimulation, respect to RVA pacing, could make the difference. In effect, basal NYHA functional class, higher in parahisian group than in control groups of patients, improved during the follow up; on the contrary, patients with high percentage RVA pacing had a NYHA class worsening (Table 3). Unfortunately, we could not collect definite informations about hospital readmission for heart failure and long-term mortality of our patients: this is another limitation to better establish the long term efficacy of parahisian septal permanent pacing.

The second main limit of the the study was the retrospective evaluation of patients; however, in every group (NO pacing, RVA pacing and SEPTAL pacing) the patients evaluated were consecutively enrolled and this could reproduce a real world situation.

Surely, the superiority of parahisian septal *vs* RVA permanent pacing should be evaluated and confirmed with a prospective multicenter study.

COMMENTS

Background

The usual way to treat symptomatic severe bradycardia is to implant an artificial pacemaker, with a stimulating lead in the apex of the right ventricle of the heart, providing electrical stimuli that generate the pulse. Unfortunately, that kind of stimulation can be detrimental in the long term, causing progressive heart failure in a number of patients. Alternative strategies were attempted: one of the most promising seems the placement of the stimulating lead in the upper region of the interventricular septum (parahisian site, near the division between right and left bundle branches), a position that can partly reproduce the physiological electrical activation of a normal heart. This kind of cardiac stimulation is called "septal parahisian pacing".

Research frontiers

The authors' group pioneered septal parahisian stimulation; the authors think

that this kind of cardiac pacing must have a wide diffusion (as an alternative to the usual way) and they provide support to their hypothesis with this paper, reporting safety and efficacy in a long term follow up.

Innovations and breakthroughs

In the past, some concerns arose about long-term safety and efficacy of septal pacing. In addition, some authors described it as difficult to perform for the traditionally trained interventional cardiologists. This paper shows that septal parahisian pacing can be easily obtained (some "tips and tricks" are provided to attempt the procedure) and that long term safety is guaranteed; in addition, better outcomes in term of exercise capacity, quality of life and cardiac function are obtained.

Applications

Patients with symptomatic severe bradycardia will benefit from a physiologic heart stimulation, if treated with septal parahisian pacing, avoiding unfavorable long term effect of the conventional electrical therapy.

Terminology

Septal parahisian (PH) pacing is a kind of cardiac stimulation that uses a transvenous lead placed in the upper region of the inter-ventricular septum, near the division between right and left bundle branches, to determine "physiological" ventricular electrical depolarization. The ejection fraction of the left ventricle is the measure commonly used to quantify cardiac function, and is negatively affected by conventional cardiac artificial pacemakers in a number of patients.

Peer-review

Very good work has been performed by Eraldo Occhetta *et al* comparing the safety, efficacy and benefits of right ventricular septal pacing *vs* right ventricular apical pacing. Congratulation to the authors for adding valuable data for the long-term superiority of septal pacing above apical stimulation.

REFERENCES

1 **Prinzen FW**, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol* 2002; **25**: 484-498 [PMID: 11991375 DOI: 10.1046/j.1460-9592.2002.00484.x]

2 **Tantengco MV**, Thomas RL, Karpawich PP. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. *J Am Coll Cardiol* 2001; **37**: 2093-2100 [PMID: 11419893 DOI: 10.1016/S0735-1097(01)01302-X]

3 **Barold SS**. Adverse effects of ventricular desynchronization induced by long-term right ventricular pacing. *J Am Coll Cardiol* 2003; **42**: 624-626 [PMID: 12932591 DOI: 10.1016/S0735-1097(03)00769-1]

4 **Karpawich PP**, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. *Pacing Clin Electrophysiol* 1999; **22**: 1372-1377 [PMID: 10527019 DOI: 10.1111/j.1540-8159.1999.tb00631.x]

5 **Tse HF**, Yu C, Wong KK, Tsang V, Leung YL, Ho WY, Lau CP. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. *J Am Coll Cardiol* 2002; **40**: 1451-1458 [PMID: 12392836 DOI: 10.1016/S0735-1097(02)02169-1]

6 **Connolly SJ**, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med* 2000; **342**: 1385-1391 [PMID: 10805823 DOI: 10.1056/NEJM200005113421902]

7 **Nielsen JC**, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. *J Am Coll Cardiol* 2003; **42**: 614-623 [PMID: 12932590 DOI: 10.1016/S0735-1097(03)00757-5]

8 **Wilkoff BL**, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002; **288**: 3115-3123 [PMID: 12495391 DOI: 10.1001/jama.288.24.3115]

9 **Sweeney MO**, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003; **107**: 2932-2937 [PMID: 12782566 DOI: 10.1161/01.CIR.0000072769.17295.B1]

10 **Goldenberg I**, Moss AJ, Hall WJ, McNitt S, Zareba W, Andrews ML, Cannom DS. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. *Circulation* 2006; **113**: 2810-2817 [PMID: 16769917 DOI: 10.1161/CIRCULATIONAHA.105.577262]

11 **Manolis AS**. The deleterious consequences of right ventricular apical pacing: time to seek alternate site pacing. *Pacing Clin Electrophysiol* 2006; **29**: 298-315 [PMID: 16606399 DOI: 10.1111/j.1540-8159.2006.00338.x]

12 **Gammage MD**. Base over apex: does site matter for pacing the right ventricle? *Europace* 2008; **10**: 572-573 [PMID: 18403386 DOI: 10.1093/europace/eun087]

13 **Francis J**, Jayesh B, Ashishkumar M, Faizal A, Mond H. Right ventricular septal pacing: has it come of age? *Indian Pacing Electrophysiol J* 2010; **10**: 69-72 [PMID: 20126592]

14 **Bristow MR**, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**: 2140-2150 [PMID: 15152059 DOI: 10.1056/NEJMoa032423]

15 **Cleland JG**, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; **352**: 1539-1549 [PMID: 15753115 DOI: 10.1056/NEJMoa050496]

16 **Yu CM**, Lin H, Fung WH, Zhang Q, Kong SL, Sanderson JE. Comparison of acute changes in left ventricular volume, systolic and diastolic functions, and intraventricular synchronicity after biventricular and right ventricular pacing for heart failure. *Am Heart J* 2003; **145**: E18 [PMID: 12766742]

17 **Moss AJ**, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; **361**: 1329-1338 [PMID: 19723701 DOI: 10.1056/NEJMoa0906431]

18 **Deshmukh P**, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation* 2000; **101**: 869-877 [PMID: 10694526 DOI: 10.1161/01.CIR.101.8.869]

19 **Zanon F**, Baracca E, Aggio S, Pastore G, Boaretto G, Cardano P, Marotta T, Rigatelli G, Galasso M, Carraro M, Zonzin P. A feasible approach for direct his-bundle pacing using a new steerable catheter to facilitate precise lead placement. *J Cardiovasc Electrophysiol* 2006; **17**: 29-33 [PMID: 16426396]

20 **Zanon F**, Barold SS. Direct His bundle and paraHisian cardiac pacing. *Ann Noninvasive Electrocardiol* 2012; **17**: 70-78 [PMID: 22537323 DOI: 10.1111/j.1542-474X.2012.00488.x]

21 **Laske TG**, Skadsberg ND, Hill AJ, Klein GJ, Iaizzo PA. Excitation of the intrinsic conduction system through his and interventricular septal pacing. *Pacing Clin Electrophysiol* 2006; **29**: 397-405 [PMID: 16650269 DOI: 10.1111/j.1540-8159.2006.00360.x]

22 **Rector TS**, Kubo SH, Cohn JH. Patients' self-assessment of their heart failure: content, reliability, and validity of a new measure, the Minnesota Living with Heart Failure questionnaire. *Heart Fail* 1987; **3**: 198-209

23 **Kindermann M**, Hennen B, Jung J, Geisel J, Böhm M, Fröhlig G. Biventricular versus conventional right ventricular stimulation

for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol* 2006; **47**: 1927-1937 [PMID: 16697307 DOI: 10.1016/j.jacc.2005.12.056]

24 **Doshi RN**, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005; **16**: 1160-1165 [PMID: 16302897 DOI: 10.1111/j.1540-8167.2005.50062.x]

25 **Lieberman R**, Grenz D, Mond HG, Gammage MD. Selective site pacing: defining and reaching the selected site. *Pacing Clin Electrophysiol* 2004; **27**: 883-886 [PMID: 15189520 DOI: 10.1111/j.1540-8159.2004.00551.x]

26 **Kronborg MB**, Mortensen PT, Gerdes JC, Jensen HK, Nielsen JC. His and para-His pacing in AV block: feasibility and electrocardiographic findings. *J Interv Card Electrophysiol* 2011; **31**: 255-262 [PMID: 21465234 DOI: 10.1007/s10840-011-9565-1]

27 **Occhetta E**, Bortnik M, Magnani A, Francalacci G, Piccinino C, Plebani L, Marino P. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. *J Am Coll Cardiol* 2006; **47**: 1938-1945 [PMID: 16697308 DOI: 10.1016/j.jacc.2006.01.056]

28 **Victor F**, Mabo P, Mansour H, Pavin D, Kabalu G, de Place C, Leclercq C, Daubert JC. A randomized comparison of permanent septal versus apical right ventricular pacing: short-term results. *J Cardiovasc Electrophysiol* 2006; **17**: 238-242 [PMID: 16643392 DOI: 10.1111/j.1540-8167.2006.00358.x]

29 **Lustgarten DL**, Calame S, Crespo EM, Calame J, Lobel R, Spector PS. Electrical resynchronization induced by direct His-bundle pacing. *Heart Rhythm* 2010; **7**: 15-21 [PMID: 19914142 DOI: 10.1016/j.hrthm.2009.09.066]

30 **Occhetta E**, Bortnik M, Marino P. Future easy and physiological cardiac pacing. *World J Cardiol* 2011; **3**: 32-39 [PMID: 21286216 DOI: 10.4330/wjc.v3.i1.32]

31 **Shimony A**, Eisenberg MJ, Filion KB, Amit G. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. *Europace* 2012; **14**: 81-91 [PMID: 21798880 DOI: 10.1093/europace/eur240]

32 **Hillock RJ**, Mond HG. Pacing the right ventricular outflow tract septum: time to embrace the future. *Europace* 2012; **14**: 28-35 [PMID: 21846639 DOI: 10.1093/europace/eur251]

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CASE REPORT

Difficult case of a trans-septal puncture: Use of a "SafeSept" guidewire

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Informed consent statement: The patient provided informed written consent prior to ablation procedure.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

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Abstract

A 69-year-old man was admitted to our center to undergo catheter ablation of paroxysmal atrial fibrillation refractory to antiarrhythmic drug therapy. This procedure required access to the left atrium through the interatrial septum. During hospitalization, the patient performed routinely pre-procedure transthoracic echocardiography and gadolinium-enhanced cardiac magnetic resonance showing a normal anatomy of both the fossa ovalis and the interatrial septum. Access to the left atrium proved difficult and several unsuccessful attempts to perform the trans-septal puncture were made under both fluoroscopy and intracardiac echocardiography guidance, even with radiofrequency energy delivery. Finally, trans-septal puncture was successfully carried out using a novel nitinol J-shaped "SafeSept" trans-septal guidewire, designed to cross the interatrial septum through the trans-septal needle thanks to a special sharp tip. Moreover, thanks to its rounded J shape that reduces the risk of atrial perforation, the "SafeSept" guidewire, when advanced into the left atrium, becomes atraumatic.

Key words: Trans-septal puncture; "SafeSept" guidewire; Atrial fibrillation; Interatrial septum; Intracardiac echocardiography

Core tip: In recent years, the number of percutaneous therapeutic techniques requiring trans-septal catheterization has increased. We present the case of a 69-year-old man with a ten-year history of paroxysmal atrial fibrillation. Access to the left atrium proved difficult and several unsuccessful attempts to perform the trans-septal puncture were made under both fluoroscopy and intracardiac echocardiography guidance, even with radiofrequency energy delivery. Finally, trans-

septal puncture was successfully performed using a novel nitinol "SafeSept" trans-septal guidewire. If the interatrial septum is thickened, scarred, fibrous, too mobile and/or aneurismal, the use of the "SafeSept" guidewire may be a safe and effective option.

Zucchetti M, Casella M, Dello Russo A, Fassini G, Carbucicchio C, Russo E, Marino V, Catto V, Tondo C. Difficult case of a trans-septal puncture: Use of a "SafeSept" guidewire. *World J Cardiol* 2015; 7(8): 499-503 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i8/499.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i8.499

INTRODUCTION

Atrial fibrillation (AF) catheter ablation is a common therapeutic approach. The access to the left atrium, required to perform the procedure, is usually achieved through the interatrial septum. Trans-septal catheterization during catheter ablation results in high success rates with low complication incidence. Failure of the trans-septal approach is often related to unfavorable anatomical features of both the interatrial septum and the fossa ovalis[1,2]. In particular cases, trans-septal puncture can prove difficult even with the support of transesophageal or intracardiac echocardiographic imaging[3,4], or using radiofrequency energy to facilitate trans-septal puncturing[5,6]. In these cases, the use of the "SafeSept" trans-septal guidewire can be a valid alternative for achieving catheterization across the interatrial septum[7].

CASE REPORT

We present the case of a 69-year-old man with a ten-year history of paroxysmal AF. One year earlier, he had undergone catheter cryoablation of a common typical atrial flutter. After the procedure, several recurrences of paroxysmal AF refractory to antiarrhythmic drug therapy were recorded. The patient was then referred to our hospital for pulmonary vein disconnection by radiofrequency ablation. The patient had never undergone a previous procedure requiring trans-septal approach or heart surgery and did not have congenital heart defects.

During hospitalization, the patient underwent a baseline electrocardiogram that showed normal sinus rhythm and an echocardiogram that demonstrated a large left atrium (Ø 54 mm). The membrane of fossa ovalis was confirmed to be intact by gadolinium-enhanced cardiac magnetic resonance imaging, performed before ablation to assess left atrium and pulmonary vein anatomy and merge morphological and electroanatomic information during AF ablation.

At first a percutaneous trans-septal puncture was attempted. A decapolar catheter was inserted *via* femoral venous approach guided by fluoroscopy into the coronary sinus. A trans-septal needle (BRK, St Jude Medical Inc.) was advanced through a long sheath (SLO, 8 F, St. Jude Medical Inc., St. Paul, MN, United States) against the septum. By a percutaneous contralateral femoral venous approach, an ultrasound catheter (AcuNav, Siemens Healthcare, Mountain View, CA, United States) was advanced for intracardiac echocardiography monitoring. This technique was used to guide the needle to the correct position against the fossa ovalis. Normal interatrial septum anatomy was observed during the positioning.

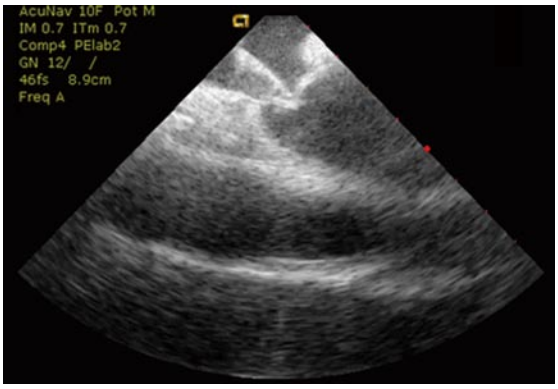

Figure 1 Intracardiac echo imaging. Correct localization of the puncture site with tenting of the fossa ovalis without crossing the interatrial septum.

Several unsuccessful attempts to obtain a trans-septal puncture were performed by two expert electrophysiologists despite changing site of puncture, needle orientation, needle types and different curved sheaths. During needle puncture, a strong resistance against the septum was encountered; both fluoroscopy and intracardiac echocardiography showed tenting of the fossa ovalis, but puncturing was not achieved despite the correct location of the needle (Figure 1).

An electrosurgical cautery generator was used to facilitate trans-septal catheterization. A standard cautery pen was placed upon the proximal portion of the trans-septal needle, then a radiofrequency pulse was delivered for few seconds at 45 W. Two unsuccessful attempts with this technique were performed.

The previous techniques were unsuccessful because of the anatomical features of the interatrial septum (*i.e.*, unusual thickness of the fossa ovalis).

In order to get a successful fossa ovalis puncture, a special trans-septal guidewire ("SafeSept" Pressure Products, Inc., United States) was considered as an option (Figure 2).

The "SafeSept" is a nitinol trans-septal guidewire designed to easily cross the interatrial septum through the trans-septal needle thanks to a special sharp tip that allows it to penetrate the fossa ovalis without the use of a particular hard contact. Moreover, the "SafeSept" is non-traumatic when advanced into the left atrium thanks to its rounded J shape, thus reducing the perforation risk of the atrial wall. The trans-septal guidewire's distal end can be easily visualized thanks to a radiopaque coil.

Figure 2 "SafeSept" trans-septal guide wire. Details of the radiopaque coil and the rounded J shape of the tip.

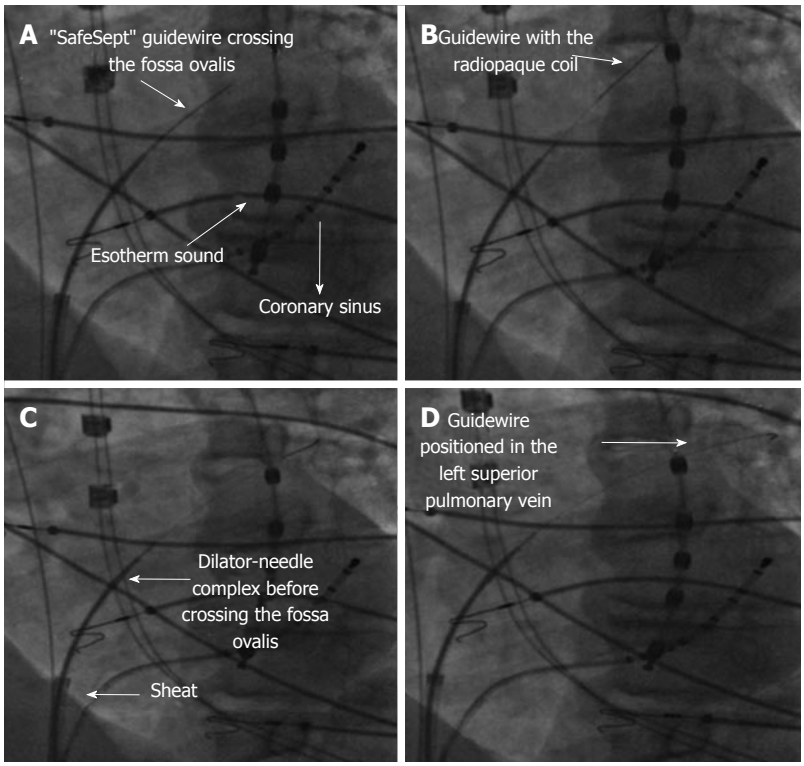

Figure 3 Sequence of fluoroscopy imaging of trans-septal puncture in the same projection (left anterior oblique view). A: The esotherm sound for the esophageal temperature control and coronary sinus catheter are in place. The "SafeSept" guidewire penetrates the fossa ovalis; B: The "SafeSept" guidewire is visible in the left atrium thanks to radiopaque coil; C: The trans-septal assembly (needle, dilator and sheath) is placed in the right atrium before crossing the fossa ovalis; D: The distal part of trans-septal guidewire is positioned in the left superior pulmonary vein.

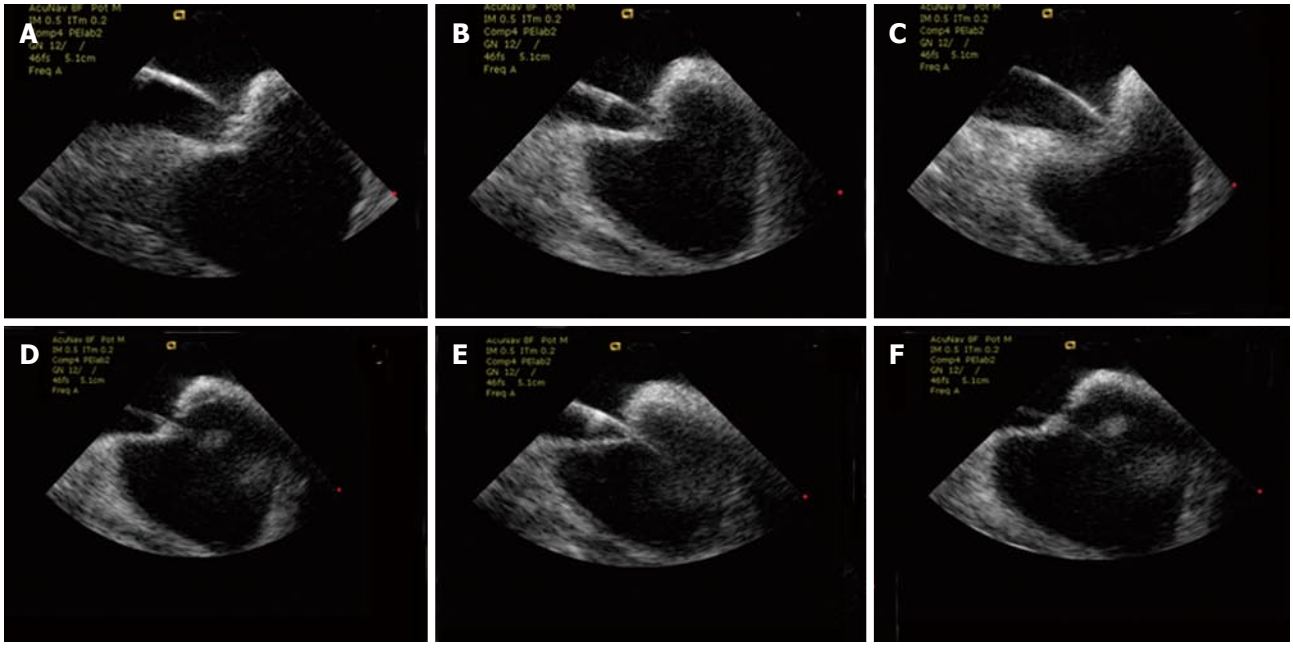

Figure 4 Sequence of intracardiac echo imaging of trans-septal puncture. The "SafeSept" guidewire is advanced through the trans-septal needle; while tenting constant force on the septum (A-C), the "SafeSept" easily crosses the fossa ovalis (D-F).

The trans-septal assembly (needle, dilator and sheath) was advanced over the guidewire. In particular, under fluoroscopic and intracardiac echo guidance, the "SafeSept" was advanced through the trans-septal needle; while tenting and maintaining constant force on the septum, the guidewire was advanced and easily crossed the interatrial septum (Figures 3 and 4). The wire (clearly visible thanks to its radiopaque coil) was further positioned in the left superior pulmonary vein.

The trans-septal needle was then advanced through the dilator and long sheath over the "SafeSept" across the fossa ovalis into the left atrium. Then the long sheath was placed in the left atrium and both trans-septal guidewire and dilator were pulled out.

Afterwards, unfractionated heparin was administered (100 U/kg) and pulmonary vein disconnection was successfully performed by radiofrequency ablation supported by the EnSite NavX electroanatomic mapping system.

DISCUSSION

In recent years the number of percutaneous therapeutic techniques requiring trans-septal catheterization has significantly increased[1,2]. The risks of complications related to perforation of the posterior atrial wall or aortic bulb remain limitations of this technique in the presence of anatomical alterations (distorted and/or thickened atrial septal tissue)[8].

Usually the trans-septal puncture is performed through fossa ovalis because it is the region offering the least resistance. This site can be located fluoroscopically and through the use of standard electrode catheters as anatomical landmarks (His region or, bulb of the aorta with a "pig-tail" catheter).

Intracardiac echocardiography was helpful to visualize the fossa ovalis in order to guide trans-septal puncture thus avoiding perforation of structures adjacent to the atrial septum or pericardial tamponade[3,4]. In the presence of unfavorable anatomy (*i.e.*, a thickened atrial septum, extremely elastic or aneurysmal fossa ovalis, presence of fibrosis due to a previous catheterization), trans-septal puncture may be challenging even with the use of these methods.

A brief application of radiofrequency to the septum, either through a dedicated radiofrequency catheter system or the use of an electrosurgical cautery pen, could be helpful in facilitating both fluoroscopy and imaging guidance[5,6].

In extremely difficult puncturing, "SafeSept" could be a valid option to cross the interatrial septum[7,9,10]. After crossing the septum, the guidewire immediately bends into a J shape, so as to be atraumatic when advanced into the left atrium. Furthermore, a radiopaque coil is positioned on the distal end of the wire to provide a fluoroscopic visualization during every step of the procedure.

In conclusion, trans-septal catheterization may be challenging if the interatrial septum is thickened, scarred, fibrous, too mobile and/or aneurysmal. The use of fluoroscopy, intracardiac ultrasound and RF energy are helpful, but may sometimes not be enough to achieve trans-septal catheterization. In these cases, the use of the "SafeSept" trans-septal guidewire may be a safe and effective option.

ACKNOWLEDGMENTS

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COMMENTS

Case characteristics

A 69-year-old man affected by palpitations with diagnosis of paroxysmal atrial fibrillation.

Clinical diagnosis

The patient had several recurrences of paroxysmal atrial fibrillation after the cryoablation of a common typical atrial flutter.

Differential diagnosis

Difficult trans-septal puncture using fluoroscopy and intracardiac echocardiography, radiofrequency energy delivery and "SafeSept" trans-septal guidewire.

Laboratory diagnosis

The patient had no alterations of hematological values.

Imaging diagnosis

Transthoracic echocardiography and gadolinium-enhanced cardiac magnetic resonance imaging showed a normal anatomy of the fossa ovalis and interatrial septum.

Pathological diagnosis

Access to the left atrium proved difficult and several unsuccessful attempts to perform the trans-septal puncture were made under both fluoroscopy and intracardiac echocardiography guidance, even with radiofrequency energy delivery.

Treatment

Trans-septal puncture was successfully carried out using a nitinol J-shaped "SafeSept" trans-septal guidewire.

Related reports

Very few cases of unsuccessful trans-septal puncture that require the use of nitinol J-shaped "SafeSept" trans-septal guidewire have been reported in the literature.

Term explanation

The novel nitinol J-shaped "SafeSept" trans-septal guidewire is designed to cross the interatrial septum through the trans-septal needle thanks to a special sharp tip but simultaneously is a non-traumatic device due to its rounded J-shape that reduces the risk of atrial wall perforation.

Experiences and lessons

Trans-septal catheterization may be challenging if the interatrial septum is thickened, scarred, fibrous, too mobile and/or aneurysmal. The use of fluoroscopy, intracardiac ultrasound and radiofrequency energy are helpful, but may sometimes not be enough to achieve trans-septal catheterization. In these cases, the use of the "SafeSept" trans-septal guidewire may be a safe and effective aid.

Peer-review

This manuscript showed a case of paroxysmal atrial fibrillation in whom SafeSept was effective for trans-septal puncture. The case is peculiar and interesting.

REFERENCES

1 **De Ponti R**, Cappato R, Curnis A, Della Bella P, Padeletti L, Raviele A, Santini M, Salerno-Uriarte JA. Trans-septal catheterization in the electrophysiology laboratory: data from a multicenter survey spanning 12 years. *J Am Coll Cardiol* 2006; **47**: 1037-1042 [PMID: 16516090 DOI: 10.1016/j.jacc.2005.10.046]

2 **Fagundes RL**, Mantica M, De Luca L, Forleo G, Pappalardo A, Avella A, Fraticelli A, Dello Russo A, Casella M, Pelargonio G, Tondo C. Safety of single transseptal puncture for ablation of atrial fibrillation: retrospective study from a large cohort of patients. *J Cardiovasc Electrophysiol* 2007; **18**: 1277-1281 [PMID: 17883403 DOI: 10.1111/j.1540-8167.2007.00958.x]

3 **Daoud EG**, Kalbfleisch SJ, Hummel JD. Intracardiac echocardiography to guide transseptal left heart catheterization for radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 1999; **10**: 358-363 [PMID: 10210498 DOI: 10.1111/j.1540-8167.1999.tb00683.x]

4 **Dello Russo A**, Casella M, Pelargonio G, Bonelli F, Santangeli P, Fassini G, Riva S, Carbucicchio C, Giraldi F, De Iuliis P, Bartoletti S, Pintus F, Di Biase L, Pepi M, Natale A, Fiorentini C, Tondo C. Intracardiac echocardiography in electrophysiology. *Minerva Cardioangiol* 2010; **58**: 333-342 [PMID: 20485239]

5 **Casella M**, Dello Russo A, Pelargonio G, Martino A, De Paulis S, Zecchi P, Bellocci F, Tondo C. Fossa ovalis radiofrequency perforation in a difficult case of conventional transseptal puncture for atrial fibrillation ablation. *J Interv Card Electrophysiol* 2008; **21**: 249-253 [PMID: 18274714 DOI: 10.1007/s10840-007-9194-x]

6 **McWilliams MJ**, Tchou P. The use of a standard radiofrequency energy delivery system to facilitate transseptal puncture. *J Cardiovasc Electrophysiol* 2009; **20**: 238-240 [PMID: 19175842 DOI: 10.1111/j.1540-8167.2008.01323.x]

7 **de Asmundis C**, Chierchia GB, Sarkozy A, Paparella G, Roos M, Capulzini L, Burri SA, Yazaki Y, Brugada P. Novel trans-septal approach using a Safe Sept J-shaped guidewire in difficult left atrial access during atrial fibrillation ablation. *Europace* 2009; **11**: 657-659 [PMID: 19363051 DOI: 10.1093/europace/eup089]

8 **Cappato R**, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2009; **53**: 1798-1803 [PMID: 19422987 DOI: 10.1016/j.jacc.2009.02.022]

9 **De Ponti R**, Marazzi R, Picciolo G, Salerno-Uriarte JA. Use of a novel sharp-tip, J-shaped guidewire to facilitate transseptal catheterization. *Europace* 2010; **12**: 668-673 [PMID: 20228079 DOI: 10.1093/europace/euq060]

10 **Wadehra V**, Buxton AE, Antoniadis AP, McCready JW, Redpath CJ, Segal OR, Rowland E, Lowe MD, Lambiase PD, Chow AW. The use of a novel nitinol guidewire to facilitate transseptal puncture and left atrial catheterization for catheter ablation procedures. *Europace* 2011; **13**: 1401-1405 [PMID: 21828065 DOI: 10.1093/europace/eur155]

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