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REVIEW

Role of gut microbiota in cardiovascular diseases

Marko Novakovic, Amit Rout, Thomas Kingsley, Robert Kirchoff, Amteshwar Singh, Vipin Verma, Ravi Kant, Rahul Chaudhary

ORCID number: Marko Novakovic (0000-0002-3419-091X); Amit Rout (0000-0002-0911-240X); Thomas Kingsley (0000-0002-6212-8988); Robert Kirchoff (0000-0001-9369-2242); Amteshwar Singh (0000-0001-7647-688X); Vipin Verma (0000-0001-5370-3146); Ravi Kant (0000-0002-9599-8082); Rahul Chaudhary (0000-0002-3276-385X).

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Marko Novakovic, Amit Rout, Department of Internal Medicine, Sinai Hospital of Baltimore, Baltimore, MD 21215, United States

Thomas Kingsley, Robert Kirchoff, Rahul Chaudhary, Department of Internal Medicine, Division of Hospital Internal Medicine, Mayo Clinic, Rochester, MN 55905, United States

Amteshwar Singh, Department of Internal Medicine, Division of Hospital Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States

Vipin Verma, Department of Internal Medicine, Medical University of South Carolina/AnMed Campus, Charleston, SC 29425, United States

Ravi Kant, Division of Endocrinology, Diabetes and Nutrition, Medical University of South Carolina/Anmed Campus, Anderson, SC 29621, United States

Corresponding author: Rahul Chaudhary, MD, FACP, Doctor, Staff Physician, Department of Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. chaudhary.rahul@mayo.edu

Abstract

The human gut is colonized by a community of microbiota, primarily bacteria, that exist in a symbiotic relationship with the host. Intestinal microbiota-host interactions play a critical role in the regulation of human physiology. Deleterious changes to the composition of gut microbiota, referred to as gut dysbiosis, has been linked to the development and progression of numerous diseases, including cardiovascular disease (CVD). Imbalances in host-microbial interaction impair homeostatic mechanisms that regulate health and can activate multiple pathways leading to CVD risk factor progression. Most CVD risk factors, including aging, obesity, dietary patterns, and a sedentary lifestyle, have been shown to induce gut dysbiosis. Dysbiosis is associated with intestinal inflammation and reduced integrity of the gut barrier, which in turn increases circulating levels of bacterial structural components and microbial metabolites, including trimethylamine-N-oxide and short-chain fatty acids, that may facilitate the development of CVD. This article reviews the normal function and composition of the gut microbiome, mechanisms leading to the leaky gut syndrome, its mechanistic link to CVD and potential novel therapeutic approaches aimed towards restoring gut microbiome and CVD prevention. As CVD is the leading cause of deaths globally, investigating the gut microbiota as a locus of intervention presents a novel and clinically relevant avenue for future research.

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Core tip: As cardiovascular diseases (CVD) remain the leading cause of mortality, this article reviews the current literature dysbiosis and its role in CVD progression to present a novel therapeutic avenue. In this paper, we provide a comprehensive review on the composition and development of gut microbiota, its changes (dysbiosis) due to endogenous and exogenous factors and the mechanistic association of dysbiosis with development of CVD. Additionally, we explore the potential therapeutic approaches focused at restoring gut microbiota and their impact on CVD.

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INTRODUCTION

The human body hosts trillions of microorganisms, and together they form an interactive ecosystem within and without outside world. The changes and interactions within this ecosystem affect the human body in health and diseases. The entourage of the associated microflora in the host is referred to as the microbiome. Majority of the microflora colonizing human body are found in the gastrointestinal tract, especially in the colon. The gut microbiota plays a major role in maintaining nutrition and immune system, which, in turn, affects the host's susceptibility and response to pathologic conditions. Imbalance in the intestinal microbiome, also known as gut dysbiosis, is associated with several conditions including gastrointestinal disorders, asthma, allergies, central nervous system disorders, metabolic syndrome, cancers and cardiovascular disease (CVD)[1,2].

CVD, a leading cause of death worldwide, stems from risk factors like smoking, lipid metabolism, diabetes and unregulated blood pressure. Atherosclerosis, the key pathophysiologic mechanism underlying the development of CVD, involves a complex interaction of vasculature, immune system and lipid metabolism. The gut microbiome affects all the component risk factors of atherosclerosis - both directly and indirectly, thus playing an important, albeit poorly understood role, in CVD[2]. In this review, we outline the role of gut microbiota in CVD and areas of future research and potential interventions.

HUMAN GUT MICROBIOTA

Composition, development and function

It is estimated that the human gut is home to approximately 1000 to 1150 microbial species[3]. The microbial gene pool has been shown to exceed the size of the human genome and is termed as metagenome[4]. The international Metagenomics of the Human Intestinal Tract Project identified the gene database of the human gut microbiome, from stool samples of 124 individuals who were healthy, overweight and obese and patients with inflammatory bowel disease. This study found 3.3 million non-redundant microbial genes, derived from 576.7 gigabases of sequence, which is approximately 150 times larger than the human genome size[3]. The two major phyla, *Bacteroidetes* and *Firmicutes* accounted for 90% of microbial species inhabiting human gut, with the rest comprised of *Actinobacteria*, *Cyanobacteria*, *Fusobacteria*, *Proteobacteria* and *Verrucomicrobia*[3,5,6].

Starting from birth, multiple factors (both intrinsic and extrinsic) affect the development of human gut microbiota pool including host genome, geography and lifestyle factors (*e.g.* diet, disease, antibiotic exposure, *etc.*) (Figure 1)[7]. In the perinatal life, maternal flora, delivery method, breastfeeding, and weaning off breastmilk affects the development of microbiome. Notably, the gut microbiota of infants

delivered vaginally consists of *Lactobacillus*, *Prevotella*, and *Atopobium*, whereas babies delivered by caesarean section predominantly carry maternal skin microflora in their guts, consisting mainly of *Staphylococcus*[8]. As the infant matures, the dominant aerobic microbiome diversifies to form an anaerobic environment, as evidenced by a high abundance of Bifidobacteria and *Clostridia* in adolescents compared to adults[9]. Interestingly, the metabolic environment of the gut changes as the microbiota evolves with age. The composition of core gut microbiota has been shown to be essentially stable throughout adulthood[9]. Changes occur with old age in accordance with the decline of physiological functions (Figure 2). As the immune system declines, an increase in facultative anaerobes, a shift in the ratio of *Bacteroidetes* to *Firmicutes* phyla, and a marked decrease in Bifidobacteria have been noted[9].

The gut microbiome plays an important function in both healthy and diseased individuals. It protects the host from epithelial cell injury and enteropathogens, regulates fat metabolism, affects the absorption of various nutrients and optimizes digestion[10,11]. The immune system is continuously modified by the introduction of components of the microbiome through the leaks in the intestinal wall. This interaction shapes the immune system, which in turn also changes the gut microbiota[7,12].

Leaky gut syndrome

Intestinal mucosal epithelial barrier, which protects the internal milieu from the hostile external environment, is maintained by the formation of tight junctions (TJs, a complex made of intramembranous proteins, occludin and several molecules from claudin family of proteins) that spread between the epithelial cells, thus creating a semi-permeable seal[13]. Lipopolysaccharides (LPS, an endotoxin) is a component of Gram-negative bacterial cell wall and is a known inducer of the inflammatory response. LPS, *via* toll-like receptors (TLRs) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, induces expression of inflammatory mediators and activates the innate immune system[14]. Higher levels of bloodstream endotoxins (especially > 50 pg/mL) have been associated with a threefold increased risk of atherosclerosis[15]. Gut microbiota is a large source of LPS, and under normal conditions with a functional intestinal barrier, it causes no harm and lower levels of LPS have been detected in healthy subjects[16,17]. In a diseased state, this barrier loses its protective function leading to increased intestinal permeability, especially to the locally produced LPS by the gut bacteria. Earlier, it was thought that leaky gut develops because of specific pathological conditions, but more recently, several studies have indicated a causal role of leaky gut rather than a consequence of the pathologic conditions[18-20]. In order to understand the role of gut microbiota in CVD, we have first to understand the factors contributing to the leaky gut syndrome.

Nutritional factors

Dyslipidemia is a known risk factor for CVD. High-energy diet and excessive fat intake are associated with significantly increased levels of LPS in blood[21,22]. Two pathways are proposed to be involved in the increased LPS with such diets - direct and indirect. In the direct pathway, food high in fat content causes an increased accumulation of chylomicrons increasing the local intercellular pressure contributing to loosening of the tight junctions. The loosening of tight junctions allows a generous influx of larger molecules such as LPS[23,24]. In the indirect pathway, the dietary fat stimulates mast cell activation in the intestinal mucosa with subsequent release of histamine and other inflammatory mediators known to increase intestinal permeability[25]. Similar to a high-fat diet, high carbohydrate intake can also lead to increased intestinal permeability and endotoxins levels[26]. With the expansion of industrial food processing, the human gut is increasingly exposed to new food additives such as nanoparticles, emulsifiers, organic solvents, and microbial transglutaminases. These products compromise the integrity of the intestinal barrier and expose the immune system to a number of foreign particles[27].

Endogenous factors

Genetic susceptibility has been implicated in several autoimmune intestinal diseases that may contribute to the leaky gut such as celiac disease and autoimmune enteropathy[28]. Zonulin is a physiological modulator of TJs and is activated by intestinal mucosa-microbiota interactions. Zonulin regulates antigen trafficking, and its upregulation in genetically susceptible individuals can lead to inflammatory and autoimmune processes[29]. Autoimmune disorders have been seen as a consequence of increased intestinal wall permeability; however, the reverse (*i.e.* autoimmune disorder causing increased intestinal wall permeability) has also been suggested in animal studies[30].

Other endogenous factors include the role of alterations in the enteric nervous

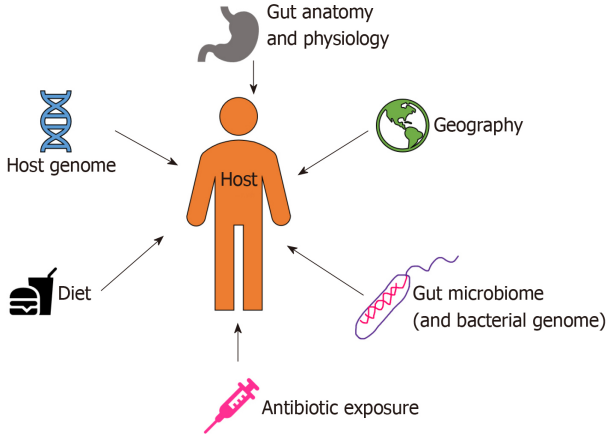

Figure 1 Factors affecting gut microbiome development.

system, and conditions compromising intestinal integrity. The enteric nervous system is a collection of neurons in the gastrointestinal tract, which functions independently from the central nervous system secreting various neurotransmitters including serotonin and histamine. In murine models, the downregulation of serotonin reuptake transporter has been associated with increased proinflammatory bowel response, increased intestinal permeability and increased fructose-induced endotoxin translocation leading to liver steatosis[31-33]. Studies have reported intestinal insult like major abdominal surgeries, shock and trauma compromises intestinal integrity as a cause or as a consequence of systemic inflammation[34].

Intestinal infections

The integrity of the intestinal barrier is also prone to many pathogen microorganisms and toxins. *Helicobacter pylori* can cause interruption of TJs by delivering cytotoxin-associated gene A, which results in loss of polarity of epithelial cells[35,36]. Enteropathogenic *Escherichia coli* secretes EspM and NIeA proteins which can induce TJ mislocalization[37,38]. *Clostridium difficile* toxin A increases paracellular permeability and translocation of zonula occludens-1 protein leading to degradation of filamentous actin[39]. TJ disruption was also implicated in cases of infection with *Vibrio parahaemolyticus* and *Salmonella enterica*[40,41].

Lifestyle factors

Chronic stress and alcohol consumption can also affect the gut microbiome. Studies suggest a key role of corticotropin-releasing factor (CRF) and its receptors (CRFR1 and CRFR2) in the pathophysiological mechanism of development of the leaky gut[42,43]. Acetaldehyde, a product of alcohol metabolism, promotes phosphorylation of tight junction proteins in the intestinal epithelium causing direct damage in addition to indirect damage by an increase in nitric oxide which damages microtubules[44]. Alcohol also alters the composition of gut microbiota with an increase in Gram-negative bacteria[44].

ROLE GUT MICROBIOTA IN CARDIOVASCULAR DISEASES

Atherosclerosis is an inflammatory disease with a growing body of evidence supporting a potential autoimmune background[45]. Infection is one of the major contributors to inflammation in the body and is a proposed mechanism of atherosclerosis. A large number of microorganisms such as *Chlamydophila pneumoniae*, *Porphyromonas gingivalis*, *Helicobacter pylori*, Influenza A virus, Hepatitis C virus, *cytomegalovirus*, and human immunodeficiency virus have been associated with an increased risk of cardiovascular diseases[46]. Infections contribute towards atherosclerosis *via* two predominant mechanisms: direct infection of the blood vessel wall (making it prone to plaque formation), or indirectly with an infection at a distant site by promoting proinflammatory mediators from a systemic immune response affect plaque growth (Figure 3)[47]. Additionally, dysbiosis also contributes to the production of atherosclerotic metabolites in the gut like trimethylamine N-oxide (TMAO) and can alter bile acid metabolism[48]. In this section, we will discuss the role and the evidence for each of the proposed mechanisms.

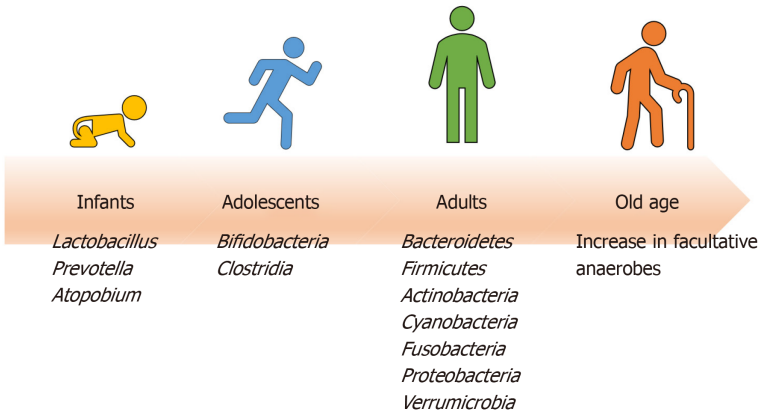

Figure 2 Evolution of gut microbiome with age and host's immune function.

Direct infection

Over 50 species of bacterial DNA have been observed in atherosclerotic plaques[49]. Proteobacteria phylum (*Chryseomonas* and *Helicobacter* genera) is found to be most abundant in atherosclerotic plaques[49]. Firmicutes phylum (*Anaeroglobus, Clostridium, Eubacterium, Lactobacillales* and *Roseburia* genera) is predominantly found in the oral and gut cavity and is also present in atherosclerotic plaques[49]. Other bacteria that have been shown to be altered in the gut among patients with atherosclerotic cardiovascular disease includes *Lactobacillales*, *Collinsella* (stenotic atherosclerotic plaques in the carotid artery leading to cerebrovascular events), *Enterobacteriaceae* and *Streptococcus* spp (Table 1)[50,51]. In fact, it has been suggested that gut microbiota, especially *Bacteroides*, *Clostridium* and *Lactobacillales* could be considered as diagnostic markers in patients suffering from coronary artery disease[52].

Indirect infection

Microorganisms, through inflammatory cytokine production and stimulation of acute-phase reactants, contribute to the development of atherosclerosis by further adding to the chronic inflammation within the atheromatous plaques[46]. In murine models, the use of antibiotics has shown an alteration in the gut microbiome, which affects carbohydrate and lipid metabolism. Initial studies investigating the role of pathogens in the development of atherosclerotic plaques had accounted for single microorganisms and not the overall microbiome, more recently it is being recognized that the aggregate number of microorganisms which an individual is colonized or infected with correlates more with atherogenesis, a concept referred to as "pathogen burden" or "infectious burden"[53].

Another possible mechanism for increased inflammation is cross-reactivity or molecular mimicry between self-antigens and bacterial antigens like heat-shock proteins and oxidized low-density lipoproteins[54]. Human heat-shock protein 60 (hHSP60) is expressed on the arterial endothelium in response to stress such as acute hypertension, hypercholesterolemia and in reperfusion injury. Also, a major antigenic component of bacteria during infection is the bacterial heat-shock protein 60s (HSP60s). Due to the high degree of homology between human and bacterial HSP, it is suggested that the antibodies formed against bacteria can target host cells expressing hHSP60. Indeed, high titres of serum antibody to mycobacterial HSP-65 were found in subjects with coronary or carotid atherosclerosis and post-myocardial infarction state[55].

As mentioned before, dysbiosis also leads to alteration in the immune system, which causes increased inflammation and atherogenesis. TLRs have been known to play a crucial role in bacterial infection and activation of the innate immune response. Once activated by ligands such as LPS, TLR dimerizes with the interleukin-1 receptor (IL-1R) forming a complex that binds myeloid differentiation primary response protein, MyD88, leading to downstream signalling cascade ultimately activating NF-κB. This cascade results in stimulation of the synthesis of proinflammatory cytokines, chemokines and costimulatory molecules[56]. TLR's expression is found in most cardiovascular cells like endothelial cells, cardiomyocytes, adventitial fibroblasts, and macrophages. Among TLRs, TLR4 is best understood. Studies have described activation of TLR4 by saturated fatty acids, acting as a ligand through the same downstream pathways as for LPS resulting in the production of proinflammatory cytokines and chemokines[57,58]. Additionally, saturated fatty acids contribute to the induction of the inflammation by alternating gut microbiota in favour of Gram-

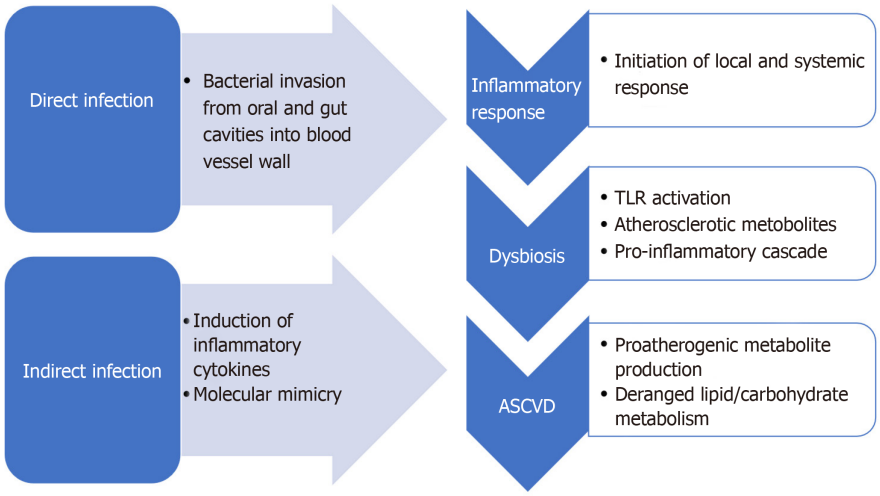

Figure 3 Proposed mechanisms of micro pathogen mediated atherosclerotic cardiovascular diseases.
ASCVD: Atherosclerotic cardiovascular diseases.

negative bacteria, thus, increasing LPS levels. These processes promote translocation of bacteria and endotoxins into the bloodstream from the intestinal lumen due to an increase in intestinal permeability, further adding to the activation of TLR4[59]. In the animal models with a genetic deficiency of TLR4 and MyD88 genes, reduced proinflammatory cytokines and decreased plaque lipid content and aortic atherosclerosis were observed[60]. Human studies have also shown increased expression of TLR1, TLR2 and TLR4 in atherosclerotic plaques, suggesting a potential role in pathogenesis[61].

Production of proatherogenic metabolites

TMAO is an intestinal microbiota metabolite of choline and phosphatidylcholine. Dietary components such as choline, phosphatidylcholine, and carnitine, found in various animal-based products and energy drinks, are metabolized by gut microbiota to trimethylamine (TMA), and then oxidized by flavin monooxidases 3 in the liver to TMAO[62,63]. Flavin monooxidases 3 is an important regulator of TMAO synthesis and is regulated by farnesoid X receptor (FXR) whose expression can be upregulated by bile acids. TMAO can lead to atherogenesis *via* multiple mechanisms, though the underlying pathway is not completely understood. It inhibits reverse cholesterol transport causing reduced cholesterol removal from peripheral macrophages, and also affects atheroprotective effects of high-density lipoprotein thus promotes atherosclerosis[64]. TMAO also acts on platelets and increases platelet hyperresponsiveness by enhancing the stimulus-dependent release of Ca^{2+} from intracellular Ca^{2+} stores leading to increased thrombotic risk[63]. The effects of TMAO have also been observed in vascular cells promoting proinflammatory protein activation such as interleukin-6, cyclooxygenase-2, intercellular adhesion molecule-1 and E-cadherin – through the NF-κB signalling pathway[65]. Tang *et al*[62] showed elevated TMAO levels were associated with increased risk of major adverse cardiovascular events, including death, myocardial infarction and stroke over a 3-year follow-up period involving more than 4000 human subjects. A strong correlation between TMAO levels and CVD was noted even after adjustments of traditional risk factors. Also, an increased risk was associated with a graded increase in TMAO levels with a significant risk of major adverse cardiovascular events seen in the highest quartile.

There are an increasing number of studies explaining the complex interplay between intestinal microflora, bile acids and metabolic disease. Bile acids affect cardiac function and play a significant, yet poorly understood, role in CVD[66]. Direct and indirect pathways have been proposed to explain their effects in CVD. In the direct pathway, bile acids have been shown to interact with cardiac myocytes affecting muscle contractility and electrical excitation. In the indirect pathway, bile acids play a significant role in lipid metabolism, plaque formation, endothelial vasodilation and neovascularization of injured organs[66]. Having been metabolized by intestinal microflora, bile acid metabolites affect different metabolic pathways through FXR-induced signalling[67]. FXR is an endogenous bile acid sensor, a member of the nuclear receptor family with chenodeoxycholic acid being its most potent ligand. FXR acts as a receptor-transcription factor which, after being bound by ligand, regulates promoter activity in a coordinated manner. In adult human tissues, FXR

Table 1 Microorganisms associated with cardiovascular disease

Microorganisms associated with cardiovascular disease
C. pneumoniae
P. gingivalis
H. pylori
Lactobacillales
Influenza A
Cytomegalovirus
Human immunodeficiency virus
Enterobacteriaceae
Streptococcus parasanguinis
Collinsella
Veillonella
Aggregatibacter
Firmicutes
Bacteroidetes
Actinobacteria
Fusobacteria
Proteobacteria
Candidate division TM7 single-cell isolate TM7c
Spirochaetes
SR1
Tenericutes
Deinococcus-Thermus
Gemmatimonadetes
Chloroflexi
Neisseria polysaccharea
Neisseria subflava
Waddlia chondrophila
Prevotella
Beggiatoa sp. P5
Alloprevotella rava
Megasphaera micronuciformis
Acidovorax sp. CF316
Atopobium parvulum
Solobacterium moorei
Clostridium difficile

expression has been found in adrenal glands, colon, liver, small intestine, kidneys and heart whereas no expression detected in brain, lung and skeletal muscles[68]. *In vitro* studies have recognized the prevention of vascular inflammation and neointimal proliferation as the potential roles FXR activation in the vascular smooth muscle cells[69].

THERAPEUTIC INTERVENTIONS: IMPROVING GUT MICROBIOME AND PREVENTING CARDIOVASCULAR DISEASE

As our understanding of the gut microbiome and its role in CVD grows, the gut microbiome is emerging as a major potential target for intervention among patients with CVD for improving clinical outcomes. The currently proposed therapeutic interventions are targeted towards the restoration of the intestinal barrier and improvement of gut microbiota. In this section, we will discuss the role of dietary modification and supplementation in the gut microbiome, followed by the possible role of faecal transplantation and targeting microbial enzyme pathways for further

prevention of CVD.

Low-fermentable oligo-, di- and monosaccharides and polyols diet

Fermentable oligo-, di- and monosaccharides and polyols group includes short-chain carbohydrates and sugar alcohols that have poor absorption in the small intestine due to osmotic activity and undergo rapid fermentation by gut microflora[70]. Studies have shown their potential therapeutic effects in diseases that are associated with increased intestinal permeability, such as non-celiac gluten sensitivity and irritable bowel syndrome[71-74]. These findings suggest their potential role in dyslipidaemias and atherosclerosis, though further investigations are warranted.

Dietary fibers/prebiotics

Whole-grain intake has been inversely associated with metabolic syndrome and mortality from CVD, independent of demographic, lifestyle and dietary factors[75]. Epidemiologic studies have also suggested a decreased risk of CVD with adequate dietary fiber intake likely through the reduction of low-density lipoprotein levels[76]. Prebiotics are fibers, mostly oligosaccharides, that are selectively fermented (mostly *Lactobacilli* and Bifidobacteria genera) and exert changes on both the composition and function of the gastrointestinal microflora to confer benefits upon host well-being and health[77]. Their proposed health benefits were observed in a mouse model, where a diet rich in various inulin-type fructans, was associated with a reduced burden of atherosclerosis[78].

Probiotics

Probiotics are live viable microorganisms (predominantly *Lactobacilli* and *Bifidobacteria*) that improve microbial balance in the gut, thus exerting positive health effects[79]. In a randomized trial, consumption of live *Lactobacillus Plantarum* was shown to diversify homogenous gut microbial flora and was associated with a reduction in incident CVD events[80]. Naruszewicz *et al*[81], in a study of 36 healthy volunteers who were active smokers showed an inverse correlation between administration of *Lactobacillus Plantarum* and blood pressure levels, fibrinogen levels, degree of adhesion of isolated monocytes and levels of proinflammatory cytokines suggesting its potential role in primary prevention of atherosclerosis. Reduced levels of low-density lipoprotein were noted in women with normal or moderately elevated cholesterol after ingestion of fermented milk containing *Lactobacillus acidophilus* and *Bifidobacterium longum*[82]. Another study found *Akkermancia muciniphila* to suppress inflammation and atherosclerotic lesion formation in the apolipoprotein E-deficient (ApoE-/-) mice. It was proposed that *A. muciniphila* reduce circulating endotoxins and improve the intestinal barrier by increasing the expression of TJ proteins[83]. Looking through the prism of intestinal microflora and gut permeability, probiotics appear to be promising protective agents, especially with regards to prophylaxis of atherosclerosis. Larger clinical trials with hard clinical outcomes are awaited for this approach to gain more credibility.

Anthocyanin

Anthocyanins represent a group of flavonoids that commonly found in fruits, vegetables, grains, and even red wine. They play a protective role against atherosclerosis after being transformed to various metabolites by gut microbiota[84,85]. Protocatechuic acid (PCA) is a metabolite derived from human gut microbiota metabolism of anthocyanin called cyanidin-3-O-glucoside[86]. PCA had been shown to inhibit atherosclerosis by reducing monocyte inflammation and adhesion in ApoE-/- mice[87,88]. PCA has also shown to decrease miR-10b expression in macrophages, which induces gene expression promoting reverse cholesterol transport contributing to regression of established atherosclerotic plaque in ApoE-/- mouse model[85]. Human studies are needed to show a clinical benefit of anthocyanin as a food supplement in the prevention of atherosclerosis.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) is described as the restoration of "healthy" functional gut microflora by administrating a faecal solution from a donor into the intestinal tract of the recipient. The beneficial effect of FMT for recurrent *clostridium difficile* infection has been proven and is now a part of the guidelines for the treatment of recurrent *clostridium difficile*. It has also been explored as a therapeutic intervention in several other pathologies such as irritable bowel syndrome, metabolic syndrome, neurodevelopmental disorders, autoimmune diseases, allergic diseases and chronic fatigue syndrome[89,90].

In a mouse model, gut microbial transplantation was conducted from the atherosclerosis-prone strain of mice and atherosclerosis–resistant strain of mice to

apolipoprotein e null mice in which resident intestinal microbes were first suppressed with antibiotics. Mice which received FMT from atherosclerosis-prone strain demonstrated choline diet-dependent enhancement in atherosclerotic plaque burden as compared with recipients of atherosclerosis-resistant strain[91]. In another study with human subjects, allogenic FMT from lean subjects to obese subjects with metabolic syndrome leads to improved insulin sensitivity and glucose metabolism[92]. The role of FMT as a secondary or primary prevention strategy to improve CVD outcomes remains to be explored with a severe limitation of its delivery method and possible complications of exposing the host to other infections.

Targeting enzyme pathways

Aortic lesions have a positive correlation with TMAO but an inverse correlation with choline levels[93]. Inhibition of FMO gene expression has been shown to reduce TMAO levels, alteration of lipid and cholesterol metabolism, and reduction in atherosclerotic lesions[94-96]. A study by Wang *et al*[97] showed that 3,3-dimethyl-1-butanol, a structural analogue of choline, inhibits microbial TMA lyases resulting in reduced TMAO levels and atherosclerotic lesion development in mice. In 2018, Roberts *et al*[98] reported the development of choline analogues iodomethylcholine and fluoro-methyl choline which can irreversibly inactivate choline TMA lyase activity. In animal models, these potent inhibitors reduced plasma TMAO levels > 95% after a single dose, for a sustained period and without any reported toxicity. The inhibitor selectively accumulated within intestinal microbes to millimolar levels, a concentration over 1-million-fold higher than needed for a therapeutic effect[98]. These studies reveal that mechanism-based inhibition of gut microbial TMA and TMAO production reduces thrombosis potential, a critical adverse complication in heart disease. They also offer a generalizable approach for the selective nonlethal targeting of gut microbial enzymes linked to host disease limiting systemic exposure of the inhibitor in the host. Despite holding significant potential, these agents still need to undergo human testing for efficacy and safety evaluation.

CONCLUSION

Gut microbiota represents an inseparable part of the human organism and remains an area of exploration in its role in the development of various pathological conditions. So far, significant progress of acknowledging our co-habitants has been made with respect to discovering its genome, functions, composition differences across different age and cultural groups. In addition, the recognition of the leaky gut syndrome has paved the way to reveal potential pathophysiological mechanisms behind numerous associations between the gut microbiota and CVD. Several factors have been identified, exogenous and endogenous, in the leaky gut and has made gut microbiome alteration a potential therapeutic target in managing several diseases including potentially CVD. However, much needs to be explored to evaluate the translation of benefits observed predominantly in animal studies to human subjects.

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REVIEW

Do age-associated changes of voltage-gated sodium channel isoforms expressed in the mammalian heart predispose the elderly to atrial fibrillation?

Emmanuel Isaac, Stephanie M Cooper, Sandra A Jones, Mahmoud Loubani

ORCID number: Emmanuel Isaac (0000-0003-0724-0106); Stephanie M Cooper (0000-0002-4357-5600); Sandra A Jones (0000-0003-4917-7264); Mahmoud Loubani (0000-0003-1826-6686).

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Emmanuel Isaac, Mahmoud Loubani, Department of Cardiothoracic Surgery, Hull University Teaching Hospitals, Cottingham HU16 5JQ, United Kingdom

Stephanie M Cooper, Sandra A Jones, Department of Biomedical Sciences, University of Hull, Hull HU6 7RX, United Kingdom

Corresponding author: Mahmoud Loubani, BM BCh, FRCS, MD, Consultant Cardiac Surgeon, Professor, Surgeon, Department of Cardiothoracic Surgery, Hull University Teaching Hospitals, Castle Road, Cottingham HU16 5JQ, United Kingdom.
mahmoud.loubani@hey.nhs.uk

Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. The prevalence of the disease increases with age, strongly implying an age-related process underlying the pathology. At a time when people are living longer than ever before, an exponential increase in disease prevalence is predicted worldwide. Hence unraveling the underlying mechanics of the disease is paramount for the development of innovative treatment and prevention strategies. The role of voltage-gated sodium channels is fundamental in cardiac electrophysiology and may provide novel insights into the arrhythmogenesis of AF. $Na_v1.5$ is the predominant cardiac isoform, responsible for the action potential upstroke. Recent studies have demonstrated that $Na_v1.8$ (an isoform predominantly expressed within the peripheral nervous system) is responsible for cellular arrhythmogenesis through the enhancement of pro-arrhythmogenic currents. Animal studies have shown a decline in $Na_v1.5$ leading to a diminished action potential upstroke during phase 0. Furthermore, the study of human tissue demonstrates an inverse expression of sodium channel isoforms; reduction of $Na_v1.5$ and increase of $Na_v1.8$ in both heart failure and ventricular hypertrophy. This strongly suggests that the expression of voltage-gated sodium channels play a crucial role in the development of arrhythmias in the diseased heart. Targeting aberrant sodium currents has led to novel therapeutic approaches in tackling AF and continues to be an area of emerging research. This review will explore how voltage-gated sodium channels may predispose the elderly heart to AF through the examination of laboratory and clinical based evidence.

Key words: Voltage-gated; Sodium channels; Ageing; Atrial fibrillation; $Na_v1.5$; $Na_v1.8$; Late sodium current; Cardiac electrophysiology

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Core tip: $Na_v1.8$ has been implicated by multiple studies in producing the late sodium current, predisposing the cardiomyocyte to arrhythmogenic activity. Animal models have demonstrated an enhancement of this aberrant current in aged hearts. Human studies have identified a reduction of $Na_v1.5$ and an increase in $Na_v1.8$ in both heart failure and left ventricular hypertrophy, strongly suggesting that voltage-gated sodium channel expression plays a central role in the development of arrhythmia. Clinically, sodium channel blockade through Ranolazine has proved promising in terminating the arrhythmia. Prevention of atrial fibrillation should focus on lifestyle management, as well as targeting cardiac risk factors. Irbesartan has been demonstrated to slow atrial remodelling, prevent atrial fibrillation in animal models, as well as avert the arrhythmia in human subjects.

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting an estimated 33.5 million people worldwide[1]. Prevalence of AF increases with age; 2.8% of the affected population under the age of 45, 16.6% between 45-65 and 80.5% aged 65 and over[2]. Altered expression of sodium channel isoforms associated with ageing has been demonstrated in animal models[3,4] though yet to be identified within the human heart. Furthermore, mutations in the *SCN5a* gene coding for the predominant $Na_v1.5$ isoform are strongly associated with a spectrum of cardiac arrhythmias including; Long QT syndrome, Brugada's syndrome and AF[5-8]. Unravelling the mechanistic processes that underlie rhythm disturbances in the pathogenesis of AF is a paramount strategic goal to enable the development of innovative therapies for both the prevention and treatment of the condition.

EPIDEMIOLOGY AND HEALTHCARE BURDEN OF AF

When age alone is considered as a major risk factor for developing AF[9], an ageing population will inevitably give rise to an increased prevalence of the arrhythmia. The European Union predicts the incidence of AF to more than double in it's over 55 populous by 2060[10]. More immediately worrying projections are estimated in the United States from 5.2 million cases in 2010 to 12.1 million by 2030[11]. AF carries significant morbidity with sufferers at notably higher risk of stroke[12], heart failure[13], myocardial infarction[14] and death[15]. Inpatient hospitalization specifically due to AF continues to rise by roughly 1% a year, placing a significant burden on healthcare resources[16].

Over five years, the direct cost of AF in the United Kingdom rose dramatically from £244 million to £458 million, taking into account hospitalisation and drug expenditure. Appreciating the cost of long term nursing home care as a consequence of the condition tallied an additional £111 million in the year 2000, more than double that in 1995[17]. Hospital care burden of AF continues to escalate around the globe with Korea claiming a rise of 420% between 2006-2015. The majority of these cases were due to major bleeding as a consequence of anticoagulation. The majority of patients were 70 years and older and the total cost of care for AF related hospital admissions rose from €68.4 million to €388.4 million over 9 years[18].

Further to the concerning rise in the prevalence of AF, placing a significant burden on healthcare resources worldwide; the consequences of current therapeutic strategies addressing the potentially fatal pro-thrombotic risks of AF, have inadvertently led to a sharp rise in hospital admissions due to adverse effects of said treatment. Appreciating the role of voltage-gated sodium channels (VGSCs) in the development of AF offers a fresh perspective on therapeutic approaches.

VOLTAGE-GATED SODIUM CHANNELS

VGSCs are transmembrane protein complexes that produce the depolarising influx of sodium ions at the initiation and duration of the action potential (AP)[19]. There are nine subtypes of VGSCs that are expressed within the mammalian class. Each isoform has specific features; activation/inactivation voltage threshold, amino acid sequence, and gene. VGSCs are expressed proportionately differently depending on the bodily tissues. The standardised nomenclature for these channels was first proposed by Goldin *et al*[20] in the year 2000. Na_v 1.1, 1.2, 1.3 and 1.6 are predominantly expressed in the central nervous system[21]. $Na_v1.4$ is dominant in skeletal muscle. Na_v 1.5 is the predominant cardiac isoform, making up nearly 90% of all sodium channel isoforms expressed in the heart; responsible for over two-thirds of the total sodium current[22]. Finally, Na_v 1.7, 1.8 and 1.9 are abundantly expressed in the peripheral nervous system[23] (Table 1).

CARDIAC SODIUM CURRENTS AND ARRYTHMOGENISIS

Fast and late sodium currents

The sodium current (I_{Na}) can be appreciated as two phases; the peak (fast) sodium current and the late (slow) sodium current (I_{NaL}). The majority of the depolarizing Na^+ current is generated by the fast I_{Na} of which $Na_v1.5$ the predominant channel responsible. This produces the AP upstroke and "maximum upstroke velocity" (V_{max}). The late sodium current is produced by a slow, steady influx of Na^+ which persists throughout the AP. These two currents determine not only the peak of the AP and velocity of depolarisation but also in shaping AP morphology through the length of the plateau phase, repolarisation and therefore the refractory period. As illustrated in (Figure 1) an enhanced I_{NaL} prolongs AP duration. This is directly linked to afterdepolarizations-a symptom of cellular electrical instability[24-26].

Afterdepolarizations

Afterdepolarisations describe the spontaneous, delayed depolarization of the cell due to abnormal ion flux during the AP. An abnormally enhanced influx of Na^+ underlies improper calcium handling leading to afterdepolarizations[25,27]. The depolarising sodium currents activate the influx of calcium through $Cav_{1.2}$ channels. This triggers a calcium-induced calcium release from the sarcoplasmic reticulum via RyR2 receptors. A key process in excitation-contraction coupling. Overloaded cytosolic Ca^{2+} must be removed by the Ca^{2+}/Na^+ exchanger[27], widely accepted although still debated, three Na+ ions move into the cell for one Ca^{2+} ion out leading to an overall positive charge and therefore a further depolarising current[25]. The late sodium current (I_{NaL}) plays a pivotal role in this pathological development[24-29]. An unusually heightened late current slows repolarization of the cell due to an uncharacteristically persistent influx of Na^+ ions maintaining a positive membrane potential. $Na_v1.8$ has been specifically implicated in this process as blocking the channel has been shown to reduce the late sodium current, suppressing the development of afterdepolarizations in the ventricular myocytes of mice and rabbits[30].

Gene mutation of the cardiac isoform in AF

Mutations in the *SCN5a* gene encoding for the $Na_v1.5$ isoform aid our understanding of cardiac sodium currents as they are strongly associated with a spectrum of cardiac arrhythmias including; Long QT syndrome, Brugada's syndrome and AF[5-8]. Mutations in the *SCN5a* gene may penetrate as either gain-of-function or loss-of-function of the $Na_v1.5$ channel (Figure 2).

Gain-of-function describes a phenomenon where the sodium influx is enhanced due to aberrant channel gating; incomplete inactivation or late inactivation of the channel at more depolarized potentials. This enhances the late current, prolonging AP duration, leading to afterdepolarizations described above[26].

Loss-of-function mutations lead to a lower expression of $Na_v1.5$ or the expression of faulty channels. Mutated channels exhibit altered functionality of the voltage-sensor domain, meaning poor availability of Na^+ ions; channels are activated at more depolarized potentials and inactivated at less depolarised potentials[31,32]. This leads to a diminished AP upstroke and slowed depolarisation of the cardiomyocyte.

With regards to AF, both loss-of-function and gain of function mutations have been identified in familial forms of the disease[6,33,34]. Loss-of-function mutations increase the risk of AF due to decelerated conduction throughout the atria as a consequence of poor Na^+ availability. Gain-of-function variants lead to hyperexcitable cardiomyocytes due to prolonged I_{NaL}.

Table 1 Properties of voltage-gated sodium channel isoforms

Voltage-gated sodium channel isoform	Tissue	Gene	Amino acid length	Activated	Inactivated	Associated β-subunit
$Na_v1.1$	Brain	*SCN1A*	2009aa (human and rat)	-33 mV	-72 mV	β_1, β_2, β_3, β_4
$Na_v1.2$	Brain	*SCN2A*	2005aa (human); 2006aa (rat)	-24 mV	-53 mV	β_1, β_2, β_3, β_4
$Na_v1.3$	Brain	*SCN3A*	1951aa (human and rat)	-23 to -26 mV	-65 to -69 mV	β_1 and β_3
$Na_v1.4$	Skeletal muscle	*SCN4A*	1836aa (human); 1840aa (rat)	-26 to -30 mV	-56 mV	β_1
$Na_v1.5$	Heart	*SCN5A*	2016aa (human); 1951aa (rat)	-47 mV	-84 mV	β_1, β_2, β_3, β_4
$Na_v1.6$	Brain	*SCN8A*	1980aa (human); 1976aa (rat)	-37.7 mV	-98 mV	β_1 and β_2
$Na_v1.7$	PNS	*SCN9A*	1977aa (human); 1984aa (rat)	-31 mV	-61 to -78 mV	β_1 and β_2
$Na_v1.8$	PNS	*SCN10A*	1957aa (human)	-16 to -21 mV	-30 mV	Not established
$Na_v1.9$	PNS	*SCN11A*	1792aa (human); 1765aa (rat)	-47 to -54 mV	-44 to -54 mV	Not established

Illustrating the standardised nomenclature, regional tissue where the isoform predominantly located, gene, amino acid length, activation and inactivation membrane potentials and associated beta subunits. PNS: Peripheral nervous system; aa: Amino acids; mV: millivolts. Adapted from Catterall *et al*[23], 2005, with permission.

Role of non-cardiac isoforms in arrhythmogenesis

$Na_v1.8$ has been identified as responsible for producing the late sodium current and consequent arrhythmia in both mouse and human subjects[26,28,30,35]. $Na_v1.8$ is coded by the *SCN10a* gene. Unlike its neuronal counterparts $Na_v1.8$ is resistant to the neurotoxin and sodium current blocker TTX- a functional similarity to the cardiac isoform. In the human chromosome, the gene is located adjacent to *SCN5a* and shares 65% of its amino acid sequence[36]. Its close genetic and functional kinship to $Na_v1.5$, coupled with a strong association in underpinning arrhythmogenic APs has made $Na_v1.8$ a target of close study in recent years[37].

From a clinical perspective, we appreciate that patients with cardiovascular risk factors and co-morbidities are more likely to develop arrhythmia[38]. The mechanistic role of VGSCs underlying this clinical observation is of great interest. Dybkova *et al*[28] at the German Centre for Cardiovascular Research demonstrate-in human left ventricular myocytes- a significant upregulation of $Na_v1.8$ coupled with reduced expression of $Na_v1.5$ in patients with heart failure. Furthermore, they illustrate that $Na_v1.8$ contributes to AP duration and inhibition decreases the late sodium current suppressing cellular proarrhythmogenic triggers[28]. This is significant as not only does this support the literature in implicating $Na_v1.8$ to the late current and arrhythmogenesis, but it also begins to identify a deeper pathophysiological process of the diseased heart and its susceptibility to arrhythmia.

The failing heart will express greater amounts of the CNS isoform which is a less excitable channel, needing a much higher membrane potential for activation (activated at-16mV to -21mV as opposed to -41mV for $Na_v1.5$). Hence cellular depolarisation is slowed. Its inactivation is at -31mV as opposed to -84mV. This difference in gating mechanics of $Na_v1.8$ allows Na+ influx during the plateau & repolarisation phase predisposing the myocyte to afterdepolarizations. The loss of $Na_v1.5$ means the availability of Na^+ through open sodium channels in phase 0 of the AP is reduced. Reduced expression of $Na_v1.5$ will mimic the effect of a loss-of-function mutation; V_{max} will be diminished with a delayed AP upstroke as illustrated in (Figure 3).

The same research group further published similar results with regards to the role of $Na_v1.8$ to the late current and the same inverse relationship of isoform expression in patients was also seen in patients with left ventricular hypertrophy[39]. The same observation of inversed VGSC expression in two separate-though closely related-disease entities offers a deeper appreciation of why patients suffering from cardiac illness are more susceptible to developing arrhythmia.

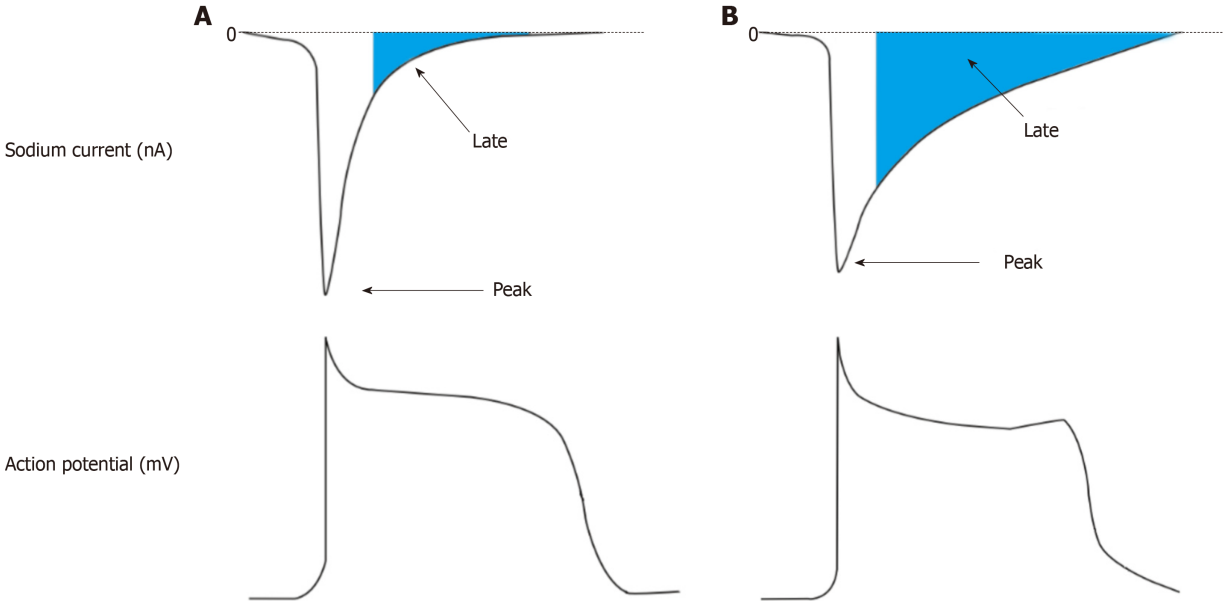

Figure 1 Peak and Late sodium currents on action potential morphology. A: Top left: An illustration of a normal sodium current within a cardiomyocyte with its rapid peak current and short late current; Bottom left: An action potential as a result of normal sodium ion influx. Plateau and repolarisation phases are not prolonged and no afterdepolarizations present; B: Top right: An Illustration of a pathologically enhanced late sodium current; Bottom right: An action potential as a consequence of enhanced late sodium current with a prolonged plateau and repolarisation period. The late upstroke between phase 2 and phase 3 represents an after depolarisation brought about due to the aberrant late sodium current. Adapted from Vadnais *et al*[74], 2010 with permission.

AGEING HEART

At a time where people are living longer than ever before, age-associated pathologies are becoming ever more commonplace in medical practice. A myriad of cardiovascular diseases are recognised to be heavily associated with the ageing heart including; AF, left ventricular hypertrophy, heart failure and ischaemic heart disease[40]. Remodelling describes the adaptation of the structure and function of the heart to allow it to meet physiological demand. During the ageing process, the heart undergoes four forms of remodelling; electrical, ionic, functional and structural[41].

AF will lead to progressive remodelling of the atria which in turn will promote abnormalities in each of these categories[42]. Functional remodelling describes the mechanical deterioration of the heart with age. This impairs the hearts central role in delivering oxygenated blood to bodily tissues. The aged heart demonstrates a decline in heart rate, reduced beat to beat variation, and significant myocardial stiffness due to fibrosis[43]. Fibrosis promotes AF due to interrupting the continuity of fibre bundles hence leading to a disruption of normal electrophysiology; impaired cell-to-cell signalling and diminished conduction velocity[44,45].

A major characteristic of electrical remodelling of the aged heart, and one central to the development of AF, is compromised pacemaker function. Sinoatrial node (SAN) loses automaticity with age due to poor excitability of SAN myocytes[46]. The loss of pacemaker function of the SAN underpins the development of ectopic focal points throughout the atria. The uncoordinated electrical firing of multiple foci means irregular contraction of the atria. Random impulses pass through the bundle of hiss to the ventricles meaning irregular ventricular contraction. This process is illustrated in the characteristic uneven baseline trace and irregularly timed QRS complexes on the electrocardiogram (ECG) of a patient with AF.

Electrophysiological remodelling leads to deviation of the normal action potential. This is ultimately underpinned through the changes of ion channel expression and function. With regards to VGSCs, Multiple sodium ion transcripts are downregulated with age leading to; shortened AP upstroke, impaired V_{max}, and prolonged AP duration[47]. Currently, there no studies comparing the expression of this channel with age in human subjects.

We know that VGSCs play a role in maintaining the plateau phase and the refractory period. The prolonged refractory period is a common feature of the elderly heart demonstrated in animal models[47,48]. A study by Baba investigating the sodium current in aged and adult canines produced contradicting results, concluding that there was no change in I_{Na} density in aged atrial cells and no structural remodelling of the fast Na^+ current with age[49]. These results stand fairly solitary contradicting a large body of evidence suggesting otherwise. Anyukhovsky *et al*[50] also carried out canine

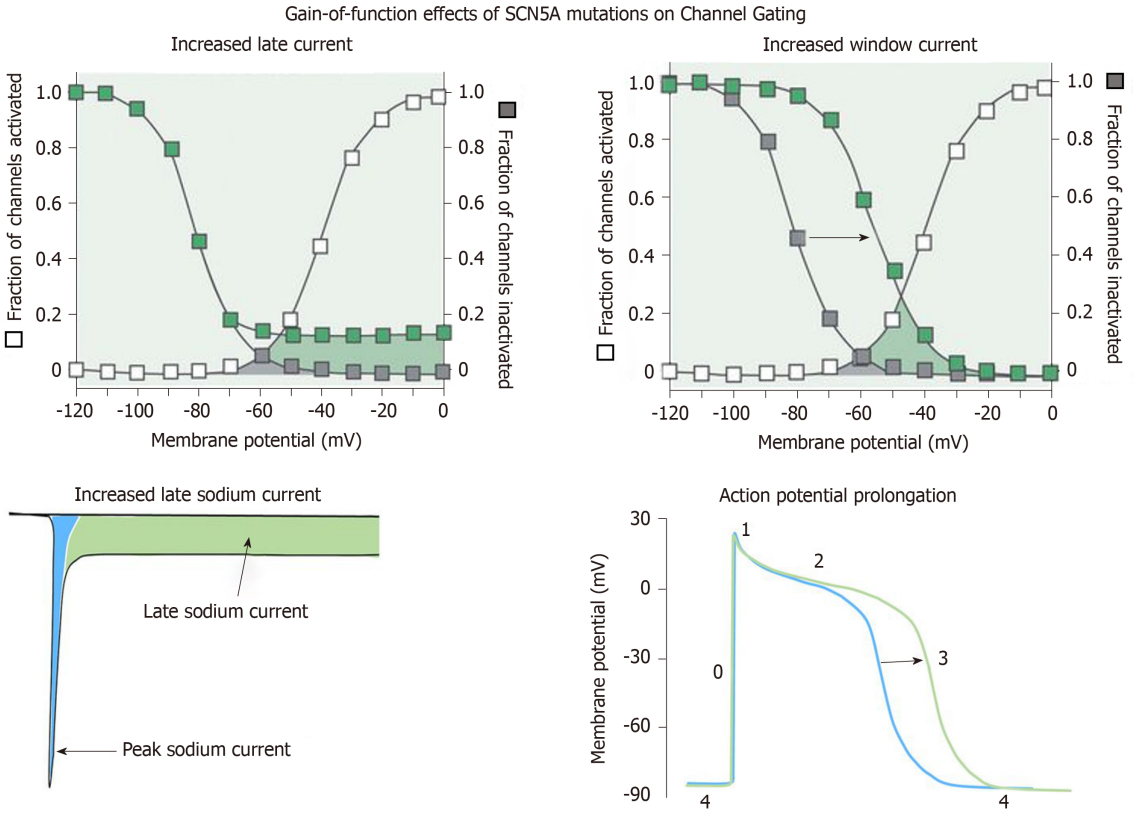

Figure 2 Gain of function effects of *SCN5a* mutations on channel gating. Top left: Curves illustrating the fraction of channels activated (white squares) and the fraction of channels inactivated (grey squares) *vs* membrane potential. Green squares demonstrate the effect of a gain of function mutation resulting in incomplete inactivation of sodium channels at higher membrane potentials. This results in a higher fraction of channels inappropriately activated for a longer period, therefore developing an enhanced late current (Bottom left); Top right: Curves illustrating the delayed inactivation of sodium channels due to gain of function mutations resulting in an increased window current where channels may reactivate, again leading to increased late current; Bottom right: A normal action potential (blue) and an action potential with a prolonged plateau and repolarisation phases (green) as a consequence of faulty sodium channel gating mechanics brought about by gain of function mutations in *SCN5a* gene leading to aberrant sodium currents. Adapted from Wilde *et al*[75], 2018, with permission.

studies investigating the effects of age and noted a significantly longer AP duration in aged dogs hence predisposing them to AF.

Currently, there is a niche within the literature for the study of the age-associated expression of cardiac sodium channels in human subjects. We would expect to see a reduction in $Na_v1.5$ and upregulation of non-cardiac isoforms, particularly $Na_v1.8$ in keeping with the literature[28,39]. Even so, the mechanisms of altered expression are poorly understood, though likely ties closely with the effect of stress age and disease places on the heart. Figure 4 shows the visual schematic representing the relative gating kinetics of $Na_v1.5$ and $Na_v1.8$.

SODIUM CHANNEL BLOCKADE AS A NOVEL THERAPUTIC TARGET FOR AF

A-803467 is a specific blocker of the $Na_v1.8$ channel. It has been successfully utilised in several studies in diminishing the I_{NaL} and restoring normal AP morphology. Furthermore, it has been demonstrated to prevent electrical remodelling and reduce the incidence and duration of paroxysmal AF in canines[51]. Blocking the 1.8 channel using this agent has also been shown to suppress ventricular arrhythmia induced via acute ischaemia[52]. Further research into the clinical use of this agent, or one of similar pharmacodynamics, is needed as results so far have only been achieved in laboratory settings.

Traditionally, pharmacological treatment for AF has mainly been focused around the use of Amiodarone (class III arrhythmic), Digoxin (cardiac glycoside), β-blockers such as Sotalol as well as calcium channel blockers Diltiazem and Verapamil. These are the drugs currently recommended for the management of AF by the National Institute for Health Care Excellence (NICE) guidelines. Sodium channel blockade is a novel therapeutic approach in the management of AF and a rapidly emerging field of research with promising clinical implications. Table 2 summarises the family of class I

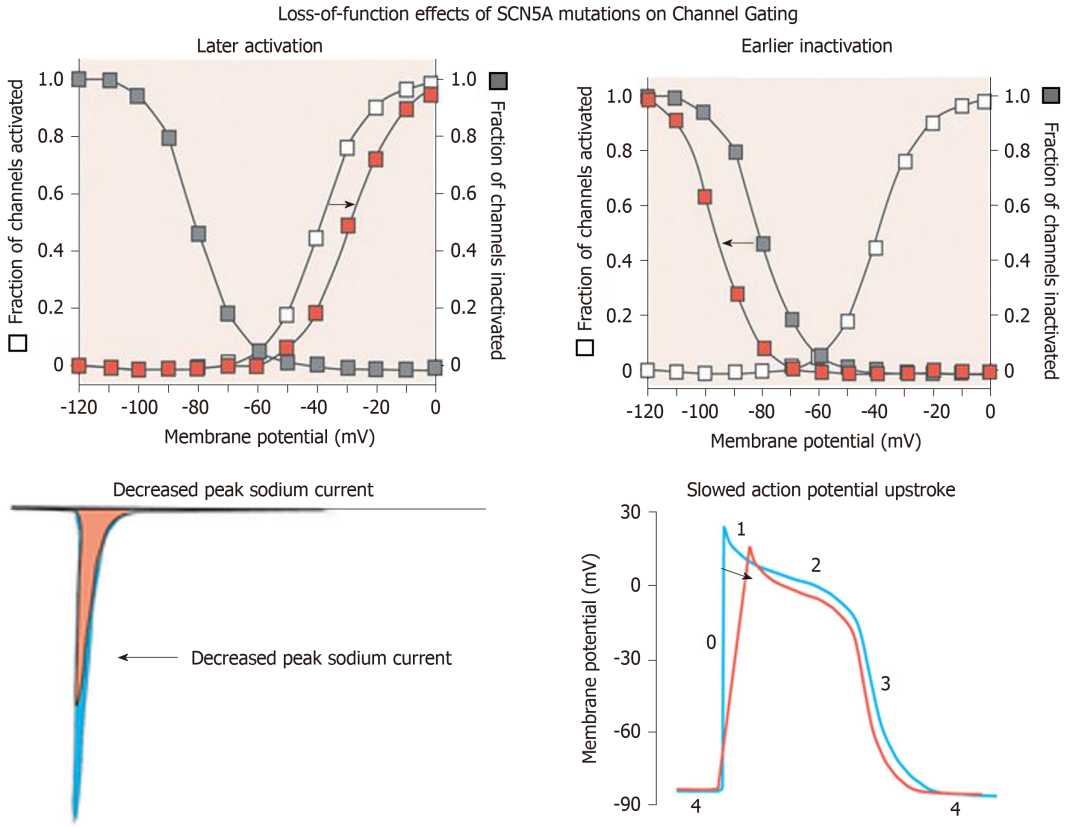

Figure 3 Loss of function effects of *SCN5a* mutations on channel gating. Top Left: Curves illustrating the fraction of channels activated (white squares) and the fraction of channels inactivated (grey squares) *vs* membrane potential. Orange squares represent the effect of loss of function mutation on channel activation, the white curve is shifted to the right demonstrating a delay; Top right: Orange squares here represent the effect of loss of function mutation on channel inactivation. The grey curve is shifted to the left demonstrating early inactivation. Both of these effects mean a reduction in Na^+ availability and a decreased peak sodium current (Bottom left); Bottom right: A normal action potential (blue) juxtaposed alongside an action potential due to a loss of function mutation (orange). Action potential upstroke is diminished and slowed. Adapted from Wilde *et al*[75], 2018, with permission.

antiarrhythmic drugs. Sodium channel blockers are more frequently used for the termination of ventricular arrhythmias as opposed to atrial tachycardia. Of the clinically available sodium channel blockers, Ranolazine is of particular interest. Multiple studies have illustrated its efficacy in terminating atrial tachyarrhythmia through specific blockade of the proarrhythmogenic late sodium current, reducing the risk of adverse electrophysiological effects.

Ranolazine is presently the only Vaughan-Williams class I antiarrhythmic drug of its kind. It is currently within the recommended NICE protocol for the treatment of stable angina[53]. It is a potent blocker of the late sodium current and also shown to mildly inhibit other ion currents such as $I_{kr,}$ and I_{ca}[54]. It is specific in not only for targeting $I_{NaL,}$ but also atrial myocytes compared to ventricular myocytes[55]. Its selectivity for the late sodium current is three times that of the peak current, demonstrating its superiority over Flecanide[56]. Its efficacy in native cardiomyocytes was just as potent as it was in experimental conditions[57,58]. A clinical trial in 2007 investigated the efficacy of Ranolazine as an anti-anginal medication. Total 6560 patients admitted with non-ST elevation myocardial infarction were randomised to receive either Ranolazine or a placebo. Patients had continuous ECG monitoring during their hospital stay. The Ranolazine group had a significantly reduced incidence of ventricular tachycardia ($P \leq 0.001$) and although the incidence of new-onset AF was low in both groups, the intervention arm also showed a statistically significant reduction compared to control[59].

Since its initial promising pre-clinical and clinical investigation, Ranolazine has continued to produce spectacular results including: terminating acutely induced AF in horses through cardioversion[60], found to be protective against AF in chronic ischaemic heart disease[61] and even effective in the conversion of postoperative AF in cardiac surgery[62]. The randomised control trial HARMONY tested the efficacy of Ranolazine in reducing "AF Burden" in patients with paroxysmal AF and those with implanted pacemakers over 12 wk. This was qualified through clinical laboratory tests, ECGs and symptom diaries. On its own it did not significantly reduce AF burden, however when paired with a moderate dose of dronedarone had a 59%

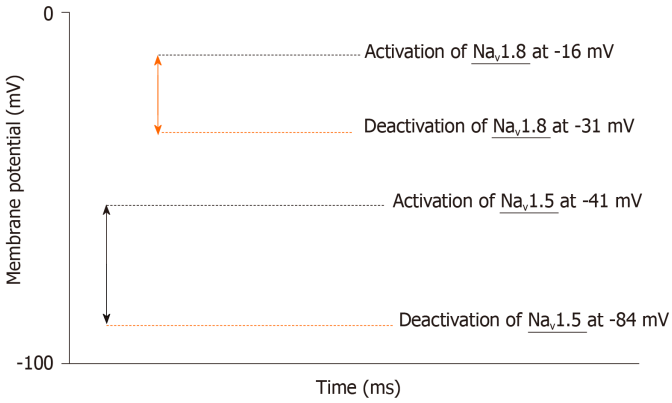

Figure 4 Visual Schematic representing the relative gating kinetics of Na$_v$1.5 and Na$_v$1.8. Na$_v$1.5 represented by the double-headed blue arrow activates at -41 mV and deactivates at -83 mV. Na$_v$1.8 represented by the double-headed orange arrow activates at -16 mV and deactivates at -31 mV.

reduction in AF burden, including fewer AF outbreaks and improved patient symptoms[63]. The clinical applications of Ranolazine continue to impress. It has been superior in and preventing and terminating post-operative AF when combined with amiodarone, compared to conventional chemical cardioversion-especially in patients undergoing coronary artery bypass grafting. In the RAFAELLO trial, 241 patients with AF who underwent electrical cardioversion received either 350 mg, 500 mg or 750 mg twice daily of Ranolazine or a placebo. Patients tolerated the drug well and the higher dose arms of the trial showed a significant reduction in AF recurrence[64].

The evidence supporting the efficacy of Ranolazine beyond that of an anti-anginal medication continues to accumulate. However, there are key questions yet to be answered regarding its clinical use. The long-term effects of the drug are still unknown due to its novelty. Also, whether it can be used as a stand-alone medication for the treatment and prevention of patients with AF-outside of a surgical context is unclear. Furthermore, the potential benefit of the drug in preventing AF in the elderly population is yet to be studied. None-the-less, Ranolazine has hugely expanded the potential for sodium channel blockade as an antiarrhythmic strategy both in pre-clinical and clinical trials.

PREVENTION OF AF

Lifestyle

Research has shed much light on the mechanics of VGSCs in arrhythmia as well as beginning to offer novel therapeutic approaches. Primary prevention strategies are much the same focusing upon common modifiable cardiac risk factors; obesity, smoking, alcohol, hypertension, hypercholesterolaemia and diabetes[65]. First and foremost, lifestyle management is the cornerstone of a healthy heart and should be the first approach to disease prevention by primary care physicians. Adherence to healthy lifestyle moderates the risk of cardiovascular disease[66] and addressing these issues early significantly reduces one's risk of AF and its consequent complications[67].

However, obesity continues to plague the western world. The United Kingdom parliament published a report in August 2019 claiming 28.7% of adults in England are obese and a further 35.6% are overweight[68]. The causes of such drastic figures are manifold and beyond the scope of this review. However, what is clear is that a concerning proportion of the population is at risk for the development of cardiac disease. Prevention should aim at tackling the root of pathology before medication becomes necessary. This holds especially true of modifiable cardiac risk factors.

In China, a recent study by Cai *et al*[69] aimed to investigate how community-based lifestyle intervention in the obese over 60 populous affected weight loss and cardiometabolic risk factors. The intervention arm of the study demonstrated significant weight loss as well as; blood pressure, waist circumference, fasting blood glucose, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterol This study demonstrates that adherence to a healthy lifestyle through community-based interventions is effective at reducing cardiovascular risk factors[69].

Medication

Failing lifestyle intervention, early detection and medical management of risk factors

Table 2 Summary of sodium channel blockers (class I antiarrhythmics)

Drug	Subclass	Pharmacological targets	Electrophysiological effects	Corresponding therapeutic mechanisms	Major clinical applications
Quinidine; ajmaline; disopyramide	Ia	$Na_v1.5$ open state; intermediate dissociation kinetics; often concomitant K+ channel block	Reduction in peak $I_{Na,}$ AP generation, increased excitation threshold; slowing of AP conduction in the atria, ventricles, and specialized conduction pathways; concomitant I_K block increasing AP duration and refractory period, increase in QT interval	(1) Reduction in ectopic ventricular/atrial automaticity; (2) Reduction in accessory pathway conduction; and (3) Increase in refractory period decreasing re-entrant tendency	SVTs, recurrent AF, VT, VF
Lidocaine; mexiletine	Ib	$Na_v1.5$ open state; rapid dissociation; window current	Reduction in peak I_{Na}, AP generation with increased excitation threshold; slowed AP conduction in the atria, ventricles and specialised ventricular conduction pathways; shortening of AP duration and refractory period in normal ventricular and Purkinje myocytes; prolongation of ERP, reduced window current in ischaemic, partially repolarised cells. Little ECG effect, slight QTc shortening	(1) Reduction in ectopic ventricular automaticity; (2) Reduction in DAD-induced triggered activity; and (3) Reduced re-entrant tendency by converting unidirectional to bidirectional block particularly In ischaemic, partially depolarised myocardium	VT and VF particularly after myocardial infarction
Propafenone; flecainide	Ic	$Na_v1.5$ inactivated state; slow dissociation	Reduction in peak I_{Na}, AP generation with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialised ventricular conduction pathways; reduced overall excitability; prolongation of APD at higher heart rates; increase in QRS duration	(1) Reduction in ectopic ventricular/atrial automaticity; (2) Reduction in DAD-induced triggered activity; and (3) Reduced re-entry tendency slowed conduction and reduced excitability particularly at rapid heart rates blocking re-entrant pathways showing depressed conduction	SVTs (atrial tachycardia, atrial flutter, AF, tachycardias involving Accessory pathways). Ventricular tachyarrhythmias resistant to other treatment in the absence of structural heart disease, premature ventricular contraction, catecholaminergic polymorphic VT
Ranolazine	Id	$Na_v1.5$ late current.	Reduction in the late Na+ current, affection AP recovery, refractoriness, repolarisation reserve and QT interval	(1) Decrease in AP recovery time; and (2) Reduction in EAD-induced triggered activity	Stable angina, VT. A new class of drug for the management of atrial tachyarrhythmias

Highlighting subclassification, pharmacological targets, electrophysiological effects, therapeutic mechanisms and clinical applications. AP: Action potential; SVT: Supraventricular tachycardia; DAD: Delayed afterdepolarizations; EAD: Early afterdepolarizations; ERP: Effective refractory period. Adapted from Lei *et al*[76], 2018, with permission.

is paramount. Irbesartan is a commonly prescribed angiotensin receptor blocker used to treat hypertension. Its renal safety profile allows for the drug to be administered to patients undergoing haemodialysis under NICE guidelines. As such, it warrants consideration for elderly patients in whom kidney function may be impaired due to age or polypharmacy. Interestingly, Irbesartan has been demonstrated to prevent sodium channel remodelling and improved intra-atrial conduction in canine models of AF[70]. Canine studies have also demonstrated its efficacy in reducing the progression of atrial fibrosis[71].

It's potential for AF suppression in human studies was investigated by the SILK study. The drug did not appear to have an advantage over Amlodipine in preventing AF recurrence in patients who have had ablation or electrical cardioversion for the

arrhythmia[72]. However, this relatively small-scale clinical trial of 98 patients already with the condition does not discredit the potential preventative benefits of the drug. A meta-analysis of randomized controlled trials tallying a total of 13184 patients found that recurrence of AF was significantly reduced in patients using angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers. Irbesartan was found to be particularly effective[73]. The collective evidence from laboratory and clinical studies suggests that Irbesartan certainly warrants consideration as a preventative strategy of AF, particularly in elderly patients where renal function may be compromised.

CONCLUSION

The role of VGSCs in cardiac arrhythmia is fundamental, proving to be an exciting and rapidly emerging field of research. In recent years much light has been shed on the role of $Na_v1.8$ in the arrhythmogenic process. New approaches targeting this channel in the treatment of arrhythmia have proved promising. To date, the emphasis of lifestyle management, and early medical intervention in the prevention of cardiac disease cannot be overstated. As we explore the mechanics of AF in both laboratory and clinical settings, our understanding of cardiac electrophysiology continues to evolve from the world of basic science through to the heart of clinical practice.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Comparative assessment of clinical profile and outcomes after primary percutaneous coronary intervention in young patients with single *vs* multivessel disease

Atif Sher Muhammad, Tariq Ashraf, Ayaz Mir, Syed Alishan, Faiza Farooq, Ali Ammar, Musa Karim, Syed Nadeem Hassan Rizvi, Tahir Saghir, Jawaid Akbar Sial, Naveed Ullah Khan

ORCID number: Atif Sher Muhammad (0000-0003-4541-9393); Tariq Ashraf (0000-0002-6680-1017); Ayaz Mir (0000-0003-2932-8475); Syed Alishan (0000-0002-6005-0961); Faiza Farooq (0000-0003-3709-3071); Ali Ammar (0000-0001-7778-4278); Musa Karim (0000-0001-7941-8191); Syed Nadeem Hassan Rizvi (0000-0001-8648-0348); Tahir Saghir (0000-0002-3148-8964); Jawaid Akbar Sial (0000-0003-3700-127X); Naveed Ullah Khan (0000-0002-3338-1642).

Author contributions: Muhammad AS, Ashraf T, Mir A, Alishan S, Farooq F, Ammar A, Karim M, Rizvi SNH, Saghir T, Sial JA, Khan NU contributed to the writing, revising of this manuscript.

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Atif Sher Muhammad, Tariq Ashraf, Ayaz Mir, Syed Alishan, Faiza Farooq, Ali Ammar, Syed Nadeem Hassan Rizvi, Tahir Saghir, Jawaid Akbar Sial, Naveed Ullah Khan, Department of Adult Cardiology, National Institute of Cardiovascular Diseases, Karachi 75510, Pakistan

Musa Karim, Department of Clinical Research, National Institute of Cardiovascular Diseases, Karachi 75510, Pakistan

Corresponding author: Atif Sher Muhammad, FCPS, MBBS, Doctor, Senior Registrar, Department of Adult Cardiology, National Institute of Cardiovascular Diseases, Rafiqui (H.J.) Shaheed Road, Karachi 75510, Pakistan. dratifsher89@gmail.com

Abstract

BACKGROUND

Even though percutaneous coronary intervention (PCI) improved the survival of patients with acute myocardial infarction, still multivessel coronary artery disease remains an important factor burdening prognosis and it is being associated with a worse prognosis compared to single-vessel disease (SVD).

AIM

To compare the clinical profile and outcomes after the primary PCI in young patients with SVD *vs* multivessel disease (MVD).

METHODS

The retrospective cohort of patients were divided into two groups: SVD and MVD group. The study population consisted of both male and female young (≤ 45 years) patients presented with ST-elevation myocardial infarction (STEMI) at the National Institute of Cardiovascular Disease, Karachi, Pakistan and undergone primary PCI from 1st July 2017 to 31st March 2018. Pre and post-procedure management of the patients was as per the guidelines and institutional protocols.

RESULTS

A total of 571 patients with STEMI, ≤ 45 years were stratified into two groups by the number of vessels involved, 342 (59.9%) with SVD and 229 (40.1%) with MVD. The average age of these patients was 39.04 ± 4.86 years. A lower prevalence of hypertension and diabetes was observed in SVD as compare to MVD group (25.1% *vs* 38%, $P < 0.01$; 11.7% *vs* 27.5%, $P < 0.001$) respectively.

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While, smoking was more prevalent among the SVD group as compare to MVD group (36.3% *vs* 28.4%, $P = 0.05$). The high-C Lesion was observed in a significantly higher number of younger patients with MVD as compared to SVD group (48.8% *vs* 39.2%, $P = 0.021$). Post-procedure thrombolysis in myocardial infarction flow grade was found to be not associated with the number of diseased vessels with a P value of 0.426 and thrombolysis in myocardial infarction flow grade III was observed in 98% *vs* 96.5% of the patients is SVD *vs* MVD group.

CONCLUSION
The MVD comprised of around 40% of the young patients presented with STEMI. Also, this study shows that diabetes and hypertension have a certain role in the pathogenesis of multivessel diseases, therefore, preventive measures for diabetes and hypertension can be effective strategies in reducing the burden of premature STEMI.

Key words: Young; Multivessel disease; Primary percutaneous coronary intervention; ST-elevation myocardial infarction; Premature coronary artery diseases; Single-vessel disease

Core tip: Premature coronary artery diseases are at rise. Multivessel disease (MVD) is associated with poor prognosis. MVD comprised of around 40.1% of the young patients with ST-elevation myocardial infarction. Prevalence of hypertension and diabetes was high in ST-elevation myocardial infarction patients with MVD. In-hospital outcomes of primary percutaneous coronary intervention were not different for patient with MVD.

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INTRODUCTION

Coronary artery disease (CAD) have been surging day by day, in the third world countries[1]. The 45 years or below is one of the globally accepted cutoff value for premature CAD[2], the cutoff value for young CAD in various studies varying from 35 to 55 years[3,4]. The field of cardiology has received great attention in the last decades with the young CAD with varying risk profiles and different prognosis and the length of severe coronary phase[5]. The ischemic coronary disease appears in young patients, generally below 40 to 45 years, when multiple coronary risk factors occur: Hyperlipidemia, diabetes mellitus, obesity, arterial hypertension, smoking and a family history of ischemic heart disease. Among the conventional risk factors of CAD, premature myocardial infarction (MI) was reported to be associated with smoking, family related history of coronary artery disease and dyslipidemia[5,6].

The worst presentation of coronary artery disease is ST-elevation MI (STEMI)[7], and primary percutaneous coronary intervention (PCI) is the guidelines recommended treatment for the patients with STEMI[8]. The primary purpose of revascularization is to open the infarct-related (culprit) artery in the setting of STEMI[9]. A significant atherosclerotic cardiovascular disease in more than one coronary artery is not an uncommon angiographic finding and in the setting of acute MI, significant atherosclerotic cardiovascular disease in multiple vessels is observed to be associated with increased complications and adverse clinical course[10-12].

Despite its prognostic importance, there is a paucity of data regarding the role of the number of vessels diseased in determining the outcome of management in young patients presenting with STEMI. Therefore, this study was conducted to carry out the comparative assessment of clinical profile and outcomes after the primary PCI in young patients with single-vessel disease (SVD) *vs* multivessel disease (MVD).

MATERIALS AND METHODS

This retrospective study was conducted after the approval of the ethical review committee of the institution (ERC-29/2019). The study population consisted of both male and female young (≤ 45 years) patients presented with STEMI at the National Institute of Cardiovascular Disease, Karachi, Pakistan and undergone primary PCI from 1st July 2017 to 31st March 2018. Data for the study were extracted from the institution database of prospectively collected National Cardiovascular Data Registry (NCDR™ CathPCI Registry®). Patients with a prior history of any cardiac-related surgery or intervention were excluded from the study. Informed consent was obtained from all the patients and all the diagnostic and primary PCI procedures were performed by the consultant cardiologists (with more than five years of experience) and only culprit artery was attempted with conventional stenting technique followed by post-dilation. Pre and post-procedure management of the patients was as per the guidelines and institutional protocols. Patient's baseline characteristics, demographic details, angiographic findings, and in-hospital outcome and complications were retrieved for this study. Patients with significant stenosis, ≥ 50%, in more than one vessesls or left main artery were labelled as MVD.

The clinical profile consisted of demographic details [gender, age (years), and body mass index (kg/m^2)], angina status within past two weeks (Canadian Cardiovascular Society angina grade), and angiographic findings [number of diseased vessels, localization of culprit lesion, lesion complexity, pre and post-procedural thrombolysis in MI (TIMI) flow grade, presence of thrombus and bifurcating lesion]. The post-procedural outcomes included death, re-infarction, heart failure, cardiogenic shock, and needed dialysis.

Statistical analysis

Statistical analysis of extracted data was performed using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States), Version 21.0. Patients were categorized into two groups *i.e.*, patients with SVD and patients with MVD (two or three vessels). Summary statistics such as mean ± SD for age (years) and body mass index (kg/m^2) and frequency and percentage for all other study variables were computed for both of the groups. The comparative assessments of results between the SVD and MVD group were performed by applying appropriate *t*-test or Mann-Whitney *U* test for continuous variables and χ^2 test or Fisher exact test for the categorical response variables. Any *P* value ≤ 0.05 was considered statistically significant.

RESULTS

A total of *n* = 571 patients with ST-segment elevation myocardial, less than and equal to 45 years were stratified into two groups by the number of vessels involved, 342 (59.9%) with SVD and 229 (40.1%) with MVD. The average age of these patients was 39.04 ± 4.86 years and a significant difference was observed in the average age of young patients in SVD group as compared to MVD group, 38.24 ± 5.18 years *vs* 40.24 ± 4.06 years ($P < 0.001$). We observed a lower prevalence of hypertension and diabetes in SVD group as compare to MVD group (25.1% *vs* 38%, $P < 0.01$) and (11.7% *vs* 27.5%, $P < 0.001$) respectively. While, smoking was more prevalent among the SVD group as compare to MVD group (36.3% *vs* 28.4%, $P = 0.05$). A positive family history of premature CAD and obesity were not significantly differed in both SVD and MVD groups. Similarly, gender and Canadian Cardiovascular Society angina grade within past two weeks were statistically insignificant in both SVD and MVD group. The baseline clinical and demographic characteristics stratified by the number of vessels involved are presented in Table 1.

The angiographic and pre-procedural characteristics stratified by the number of vessels involved are presented in Table 2. Culprit left anterior descending artery occurred in a significantly higher number of patients in single vessel as compare to multivessel groups (71.9% *vs* 50.2%), while, culprit right coronary artery (RCA) and circumflex artery (LCX) were more frequent in patients with MVD as compared to SVD, (34.5% *vs* 21.3%) and (12.7% *vs* 5.3%) respectively. The high-C Lesion was observed in a significantly higher number of younger patients with MVD as compared to SVD group (48.8% *vs* 39.2%, $P = 0.021$).

Post-procedure outcomes stratified by the number of vessels involved are presented in Table 3. Post-procedure TIMI flow grade was found to be not associated with the number of diseased vessels with a *P* value of 0.426 and TIMI flow grade III was observed in 98% *vs* 96.5% of the patients is SVD *vs* MVD group. In-hospital mortality rate was 1.7% *vs* 0.9%, $P = 0.335$, for MVD and SVD group respectively.

Table 1 Baseline clinical and demographic characteristics stratified by number of vessels involved, *n* (%)

Characteristics	Total	Involved vessels		*P* value
		Single vessel	Multivessel	
Total	571	342 (59.9)	229 (40.1)	-
Clinical characteristics				
Age (mean ± SD, yr)	39.04 ± 4.86	38.24 ± 5.18	40.24 ± 4.06	< 0.001
Body mass index (mean ± SD, kg/m^2)	26.24 ± 4.01	26.25 ± 4.07	26.22 ± 3.94	0.929
Male gender	501 (87.7)	303 (88.6)	198 (86.5)	0.446
Hypertension	173 (30.3)	86 (25.1)	87 (38)	0.001
Diabetes	103 (18)	40 (11.7)	63 (27.5)	< 0.001
Positive family history	41 (7.2)	27 (7.9)	14 (6.1)	0.419
Smoking	189 (33.1)	124 (36.3)	65 (28.4)	0.050
Obesity	89 (15.6)	55 (16.1)	34 (14.8)	0.690
CCS angina grade (within past two weeks)				
No symptoms, no angina	272 (47.6)	158 (46.2)	114 (49.8)	0.367
CCS I	33 (5.8)	22 (6.4)	11 (4.8)	
CCS II	66 (11.6)	35 (10.2)	31 (13.5)	
CCS III	105 (18.4)	70 (20.5)	35 (15.3)	
CCS IV	95 (16.6)	57 (16.7)	38 (16.6)	

CCS: Canadian Cardiovascular Society.

Similarly, post-procedure in-hospital rate of cardiogenic shock, heart failure, and dialysis were observed higher MVD group as compared to SVD group, but not statistically significant.

DISCUSSION

To the best of our knowledge, this study is first of its kind in Pakistani young population. Aim of this study was to assess the differences in clinical profile and outcomes after primary PCI in young patients with SVD *vs* MVD. Main findings of our study are, 40.1% (229) young patients presented with STEMI had MVD. The MVD in young patients was found to be associated with age (years), hypertension, and diabetes mellitus, whereas, SVD were found to be associated with smoking. Young patients with MVD were more likely to have the angiographic finding of culprit RCA and LCX as against left anterior descending artery for the young patients with SVD and more likely to have high/C lesions. Post-procedure in-hospital outcomes among young patients were not significantly different between SVD and MVD patients, however, mortality and other complications, such as cardiogenic shock, heart failure, or dialysis, were relatively more frequent among patients with MVD.

In our study the prevalence of MVD was 40.1% among the young (≤ 45 years) patients presenting with STEMI, similarly, a recently published local study by Batra *et al*[13] reported MVD in 38% of young (≤ 40 years) patients diagnosed with STEMI. Noor *et al*[14] reported MVD in 36.6% among the patients under 35 years of age presented with acute coronary syndrome (ACS) and another study by Anjum *et al*[15] reported 28% of young (≤ 35 years) patients with MVD among patients presented with ACS. In our population, MVD reported increasing with age and severity of presentation. Studies from the various parts of the world reported MVD ranging from 16% to 55.6% of the young patients with ACS depending on the cutoff value of age for the classification of young[16-21].

Batra *et al*[11] reported that MVD was a predictor of increased morbidity and mortality in patients undergoing primary PCI for STEMI. Although, MVD is observed to be less frequent in cases of premature CAD patients[13], however, it is important to understand its association with risk factors in order to control the burden of disease in productive years of life. In our study MVD in young was found to be associated with relatively older age, 40.24 ± 4.06 years *vs* 38.24 ± 5.18 years ($P < 0.001$). However, this wasn't the case in various other parts of the world[18,19]. It was reported that diabetes mellitus and hypertension were less commonly observed risk factors among young

Table 2 Angiographic and pre-procedural characteristics stratified by number of vessels involved, *n* (%)

Characteristics	Total	Involved vessels		*P* value
		Single vessel	Multivessel	
Total	571	342 (59.9)	229 (40.1)	-
Culprit vessel				
Left anterior descending artery	361 (63.2)	246 (71.9)	115 (50.2)	< 0.001
Right coronary artery	152 (26.6)	73 (21.3)	79 (34.5)	
Circumflex artery	47 (8.2)	18 (5.3)	29 (12.7)	
Posterior descending artery	6 (1.1)	3 (0.9)	3 (1.3)	
Left main	5 (0.9)	2 (0.6)	3 (1.3)	
Pre-procedure TIMI flow grade				
TIMI - 0	321 (56.2)	185 (54.1)	136 (59.4)	0.066
TIMI - 1	58 (10.2)	38 (11.1)	20 (8.7)	
TIMI - 2	111 (19.4)	61 (17.8)	50 (21.8)	
TIMI - 3	81 (14.2)	58 (17)	23 (10)	
Lesion complexity				
Non-high/non-C lesion	325 (56.9)	208 (60.8)	117 (51.1)	0.021
High/C lesion	246 (43.1)	134 (39.2)	112 (48.9)	
Thrombus presence				
No	102 (17.9)	58 (17)	44 (19.2)	0.491
Yes	469 (82.1)	284 (83)	185 (80.8)	
Bifurcation lesion				
No	427 (74.8)	254 (74.3)	173 (75.5)	0.731
Yes	144 (25.2)	88 (25.7)	56 (24.5)	

TIMI: Thrombolysis in myocardial infarction.

patients[13], but both have significant associations with MVD[11]. Similar to these past findings, in our study, we observed that MVD in young STEMI patients was significantly associated with hypertension, and diabetes mellitus with 27.5% *vs* 11.7%, $P < 0.001$ and 38% *vs* 25.1%, $P < 0.01$ respectively.

In our study angiographic findings of culprit RCA (34.5% *vs* 21.3%) and LCX (12.7% *vs* 5.3%) were more common in young patients with MVD as compared to SVD and these were the similar observations made for young as well as entire STEMI patients in the past studies[11,18,19]. Similarly, MVD among young is found to be associated with poor pre-procedural TIMI flow grade and complex (high C) lesions.

The presence of MVD is a prognostic indicator for the patients undergoing primary PCI[11], whoever, despite multiple investigations the mechanism behind its prognostic value is unexplained. MVD was reported to be associated with the increased use of contrast volume (172.46 ± 28.39 mL *vs* 150.25 ± 33.2 mL, $P < 0.001$)[11], which increases the risk of post-procedural morbidities including contrast-induced acute kidney injury. Continuing the observations made by Anello *et al*[18], in our study post-procedural in-hospital outcomes of primary PCI for STEMI were not significantly different for young patients with MVD as compared to SVD. However, MVD patients tends to have relatively higher rate of in-hospital mortality (1.7% *vs* 0.9%, $P = 0.355$), cardiogenic shock (0.9% *vs* 0.0%, $P = 0.083$), heart failure (0.9% *vs* 0.0%, $P = 0.083$), and dialysis (0.4% *vs* 0.0%, $P = 0.221$).

The most recent evidence suggests that as against the culprit vessel only strategy, multivessel PCI or complete revascularization in STEMI patients with MVD was superior with reduced risk of re-infarction or cardiovascular mortality[22]. However, more targeted research efforts are required in young patients to ensure the early returning to work.

In conclusion, MVD comprised of around 40.1% of young patients (≤ 45 years) presented with STEMI. It was found to be associated with age, hypertension, and diabetes mellitus. In-hospital outcomes of primary PCI in patients with MVD were not significantly different from the patients with SVD. Also, this study shows that diabetes mellitus and hypertension have a certain role in the pathogenesis of MVD in young patients, preventive measures for diabetes mellitus and hypertension can be

Table 3 Post-procedure outcomes stratified by number of vessels involved, *n* (%)

Characteristics	Total	Involved vessels		*P* value
		Single vessel	Multivessel	
Total	571	342 (59.9)	229 (40.1)	-
Contrast volume (mL)	135.65 ± 44.28	134.3 ± 42.97	137.66 ± 46.18	0.375
Fluro time (min)	13.2 ± 6.69	12.83 ± 6.53	13.75 ± 6.91	0.107
Number of stents deployed	1.09 ± 0.66	1.01 ± 0.44	1.21 ± 0.87	< 0.001
Post-procedure TIMI flow grade				
TIMI - 0	3 (0.5)	2 (0.6)	1 (0.4)	0.426
TIMI - 1	3 (0.5)	2 (0.6)	1 (0.4)	
TIMI - 2	9 (1.6)	3 (0.9)	6 (2.6)	
TIMI - 3	556 (97.4)	335 (98)	221 (96.5)	
Post-procedure in-hospital outcomes				
Composite adverse events	11 (1.9)	6 (1.8)	5 (2.2)	0.715
Re-infarction	3 (0.5)	3 (0.9)	0 (0)	0.155
Cardiogenic shock	2 (0.4)	0 (0)	2 (0.9)	0.083
Heart failure	2 (0.4)	0 (0)	2 (0.9)	0.083
Dialysis	1 (0.2)	0 (0)	1 (0.4)	0.221
Mortality	7 (1.2)	3 (0.9)	4 (1.7)	0.355

TIMI: Thrombolysis in myocardial infarction.

effective strategies in reducing the burden of premature CAD.

ARTICLE HIGHLIGHTS

Research background

Even though percutaneous coronary intervention (PCI) improved the survival of patients with acute myocardial infarction, the multivessel coronary artery disease remains an important factor burdening prognosis, and it is being associated with a worse prognosis compared to single-vessel disease (SVD).

Research motivation

Despite its prognostic importance, there is a paucity of data regarding the role of the number of vessels diseased in determining the outcome of management in young patients presenting with ST-elevation myocardial infarction (STEMI).

Research objectives

This study was conducted to carry out the comparative assessment of clinical profile and outcomes after the primary PCI in young patients with SVD *vs* multivessel disease (MVD).

Research methods

Patients were divided into SVD and MVD group. The study population consisted of both male and female young (≤ 45 years) patients presented with STEMI and undergone primary PCI from 1st July 2017 to 31st March 2018. Pre and post-procedure management of the patients was as per the guidelines and institutional protocols.

Research results

A total of 571 patients with STEMI (≤ 45 years) were stratified into two groups by the number of vessels involved. The average age of these patients was 39.04 ± 4.86 years. A lower prevalence of hypertension and diabetes was observed in SVD as compare to MVD group. Smoking was more prevalent among the SVD group as compare to MVD group. The high-C Lesion was observed in a significantly higher number of younger patients with MVD as compared to SVD group. Post-procedure thrombolysis in myocardial infarction flow grade was found to be not associated with the number of diseased vessels and thrombolysis in myocardial infarction flow grade III was observed in 98% *vs* 96.5% of the patients (SVD *vs* MVD group).

Research conclusions

The MVD comprised of around 40% of the young patients presented with STEMI. Also, this study shows that diabetes mellitus and hypertension have a certain role in the pathogenesis of MVD in young patients, preventive measures for diabetes mellitus and hypertension can be effective strategies in reducing the burden of premature coronary artery disease.

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ORIGINAL ARTICLE

Observational Study

Autonomic laterality in caloric vestibular stimulation

Mohammadreza Aghababaei Ziarati, Mohammad Hosein Taziki, Seyed Mehran Hosseini

ORCID number: Mohammadreza Aghababaei Ziarati (0000-0002-2928-1200); Mohammad Hosein Taziki (0000-0001-6288-4663); Seyed Mehran Hosseini (0000-0002-4783-7428).

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Mohammadreza Aghababaei Ziarati, Department of Internal Medicine, Medical Faculty, Golestan University of Medical Sciences, Gorgan 4934174515, Golestan, Iran

Mohammad Hosein Taziki, Department of Otolaryngology, Medical Faculty, Golestan University of Medical Sciences, Gorgan 4934174515, Golestan, Iran

Seyed Mehran Hosseini, Department of Physiology, Medical Faculty, Golestan University of Medical Sciences, Gorgan 4934174515, Golestan, Iran

Seyed Mehran Hosseini, Neuroscience Research Center, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan 4934174515, Golestan, Iran

Corresponding author: Seyed Mehran Hosseini, MD, PhD, Associate Professor, Department of Physiology, Neuroscience Research Center, Gorgan Faculty of Medicine, Golestan University of Medical Sciences, Shastkola, Gorgan 4934174515, Golestan, Iran. hosseini@goums.ac.ir

Abstract

BACKGROUND

Caloric stimulation of the vestibular system is associated with autonomic response. The lateralization in the nervous system activities also involves the autonomic nervous system.

AIM

To compare the effect of the right and left ear caloric test on the cardiac sympathovagal tone in healthy persons.

METHODS

This self-control study was conducted on 12 healthy male volunteers. The minimal ice water caloric test was applied for vestibular stimulation. This was done by irrigating 1 milliliter of 4 ± 2 °C ice water into the external ear canal in 1 s. In each experiment, only one ear was stimulated. For each ear, the pessimum position was considered as sham control and the optimum position was set as caloric vestibular stimulation of horizontal semicircular channel. The order of right or left caloric vestibular stimulation and the sequence of optimum or pessimum head position in each set were random. The recovery time between each calorie test was 5 min. The short-term heart rate variability (HRV) was used for cardiac sympathovagal tone metrics. All variables were compared using the analysis of variance.

RESULTS

After caloric vestibular stimulation, the short-term time-domain and frequency-domain HRV indices as well as, the systolic and the diastolic arterial blood pressure, the respiratory rate and the respiratory amplitude, had no significant

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changes. These negative results were similar in the right and the left sides. Nystagmus duration of left caloric vestibular stimulations in the optimum and the pessimum positions had significant differences (*e.g.*, 72.14 ± 39.06 *vs* 45.35 ± 35.65, $P < 0.01$). Nystagmus duration of right caloric vestibular stimulations in the optimum and the pessimum positions had also significant differences (*e.g.*, 86.42 ± 67.20 *vs* 50.71 ± 29.73, $P < 0.01$). The time of the start of the nystagmus following caloric vestibular stimulation had no differences in both sides and both positions.

CONCLUSION
Minimal ice water caloric stimulation of the right and left vestibular system did not affect the cardiac sympathovagal balance according to HRV indices.

Key words: Caloric stimulation; Heart rate variability; Vestibular system; Autonomic; Laterality

Core tip: The caloric test can induce an isolated and unilateral stimulation of the vestibular system and can be considered as a model for studying the concept of the laterality of vestibulo-autonomic reflex. In contrast to microgravity methods or tilt test, the caloric test can provide specific data because it does not cause hemodynamic compensatory responses due to orthostasis.

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INTRODUCTION

The vestibular system provides sensory information for static and dynamic balance of the body. The physiological stimuli of the vestibular system are linear and angular accelerations. The effect of the vestibular system on the autonomic nervous system activity is generally called vestibulo-sympathetic reflex[1-5]. It is also known as the vestibulo-autonomic reflex[6]. A well-documented example of this reflex is the open-loop feedforward control of blood pressure during orthostatic challenges[7-9]. But any active or passive orthostatic challenges or body movements in addition to the vestibular system also stimulates a variety of mechanical receptors in the muscles and the cardiovascular system. These sensory signals are distributed in the brain stem and other parts of the central nervous system and may affect the autonomic tone[10-14]. In order to eliminate these movement induced effects from vestibulo-sympathetic reflex, the vestibular system must be stimulated by non-physiological methods like sound, vibration, caloric test and galvanic stimulation[15-19]. Caloric test is one of the most useful laboratory methods to determine the response of the labyrinth. It is also one of the few methods that allow the assessment of one labyrinth independent of the other[20-23]. In vestibular epithelium the slow or type II sensory cells are more responsive to caloric test[24]. The caloric test specifically stimulates the lateral or horizontal semicircular duct. There are two reasons for this phenomenon. The first reason is the closeness of this duct to the thermal stimulus in the outer ear. The second reason is the position of this duct in the same direction of thermal convections in the outer ear duct during caloric test. Vestibular stimulation in the caloric test has two mechanisms. One of them is a direct effect of temperature on vestibular afferents and/or receptors. This mechanism is independent of the head position and it matters less in quantity. The second and first-known mechanism is due to endolymph convection which is depended on the head position. The optimum position means the head is flexed 30 degrees forward in the supine position. This position puts the horizontal semicircular ducts in vertical or gravity plane. The pessimum position means the head is extended 60 degrees backward in the supine position. This position puts the horizontal semicircular ducts in the horizontal plane and eliminates the effect of gravity on endolymph convection (Figure 1).

Caloric stimulation of vestibular system is associated with autonomic response[25-27].

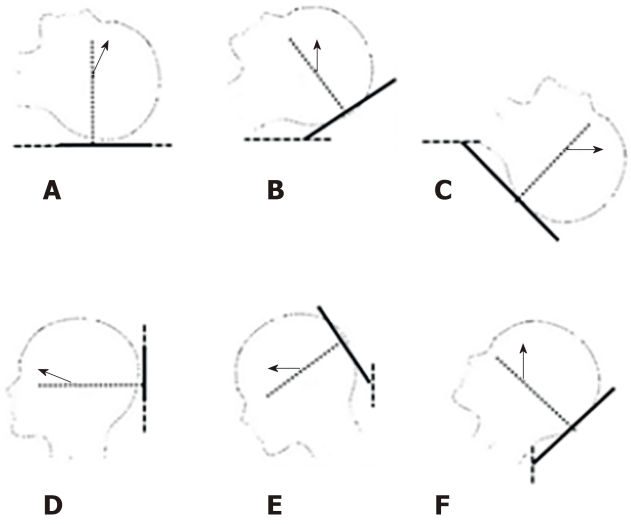

Figure 1 Schematic drawing of horizontal semi-circular canal axis and its alignment with gravity plane in supine and upright orientations. A: Arrow shows the angle between horizontal canal and vertical line in supine position; B: Arrow shows the vertical position of horizontal canal following the 30˚ forward tilt in supine position *e.g.*, the optimum position in supine state; C: Arrow shows the horizental position of horizontal canal following the 60˚ backward tilt in supine position *e.g.*, the pessimum position in supine state; D: Arrow shows the angle between horizontal canal and horizental line in upright position; E: Arrow shows the horizental position of horizontal canal following the 30˚ forward tilt in upright position *e.g.*, the pessimum position in upright state; F: Arrow shows the vertical position of horizontal canal following the 60˚ backward tilt in upright position *e.g.*, the optimum position in upright state. In optimum position the horizontal canal axis is vertical and in the gravity plane (B and F). In pessimum position this axis is horizontal and eliminates the effect of gravity on endolymph convection (C and E).

Similarly some of these autonomic effects are related to changes in skin temperature or the activation of other sensory afferents and are unrelated to stimulation of vestibular system[28]. However, head positioning to some extent can unmask the vestibular from the non-vestibular or thermoreceptors-induced autonomic effect, at least theoretically.

The lateralization in the nervous system activities also involves the autonomic nervous system[29-31]. In the review of available literature and databases, we cannot find any report about the autonomic laterality of the caloric test in normal participants. There are many reports about the differences in caloric test response parameters between right and left ear, for example, the duration and the time of onset or offset of nystagmus or the speed of its slow or fast phases. However, it is well documented that the caloric test may induce asymmetric stimulation and its output or the vestibulo ocular reflex has an inter-aural difference. The reasons for these asymmetric responses are generally attributed to the variation in the shape or in the size of external ear canals or middle ear as well as to the coplanarity of canals[32-36].

However, the lateralization may also play a role in caloric test outcomes including its autonomic effects. In this self-control study, we compared the effect of the caloric test on the cardiac sympathovagal tone in healthy persons in two states, the optimum and the pessimum positions, then the difference between the right and the left caloric vestibular stimulations on heart rate variability (HRV) were evaluated.

MATERIALS AND METHODS

This self-control study was conducted on 12 healthy male volunteers. The study protocol was confirmed by the research council of Golestan University of Medical Sciences. The ethic number was ir.goums.REC.1396.275. The subjects underwent the general clinical and otoscopic examination. They had no drug history. None of them were smokers. They had no history of chronic illness or hospitalization last year. All participants were informed about the study and assigned the informed consent. There was not any exclusion of the case from this study because of a closed ear canal, rigid ear wax, rupture of the tympanum, a history of Dizziness, vertigo, tinnitus, spontaneous nystagmus, deviation of the visual axis and eye movement disorders. All experiments were performed in the morning and between 10 h and 12 h. The volunteers were fasting at least 3 h before the experiment. The caloric test was

performed in the supine position in a dim-light room. Each ear was tested twice, in forward or optimum and in backward or pessimum bending modes, as shown in Figure 2. The order of right or left ear vestibular stimulation was randomly assigned for each volunteer. The sequence of the forward or backward head bending for the caloric test was also randomly assigned for every volunteer. This was done to reduce the conditioning effect of the first caloric test experience on the results of the next caloric tests on the same subject. The recovery time between each calorie test was 5 min. The one-milliliter ice water caloric test was applied for vestibular stimulation. In this method, cold induction was performed with 1 milliliter of ice water at about 4 °C in 1 s[34,37]. After stable positioning of the head in the optimum or the pessimum positions, the head was transiently turned laterally to put the external ear channel in the proper place for ice water irrigation and 2-3 s following the infusion phase of the caloric test, the head was then turned to its recording position. During recording, the subjects were asked to do mental tasks. This was done to reduce the subject's focus on vestibular stimulation and to prevent central inhibition of the nystagmus. The start of the nystagmus and its duration were visually monitored because of a lack of video-oculography and electronystagmography equipment in our lab. Respiration and electrocardiograph were recorded continuously by PowerLab recorder 8/30 ML870 and Dual Bio/Stim ML 408, AD Instrument Ltd. Australia. The sampling rate was 1 kHz. The lead II electrocardiograph signals were used for data analysis in successive 5 min after the caloric test. HRV was measured in time domain and frequency domain methods. The power spectrum was calculated using the fast-Fourier transformation. Three frequency bands were selected: very-low-frequency (VLF) band (0.003-0.04 Hz), low-frequency (LF) band (0.04-0.15 Hz), and high-frequency (HF) band (0.15-0.4 Hz). For overcoming the effect of total power inequality on the absolute value of LF and HF components, the spectral densities were normalized on the basis of the very-low frequency component. The normalized value of LF and HF were calculated according to the following equation: [LF or HF (ms^2)]/ [total power (ms^2)-very-low-frequency (ms^2)] and were used for statistical analysis[38].

The variables were compared using the analysis of variance before and after the caloric tests (Figure 2). The statistical review of the study was performed by Dr. Mohamd Fayaz, the biomedical statistician in Shahid Beheshti University of Medical Sciences, Tehran, Iran.

RESULTS

The mean ± SD of age, weight, and height of participants were 28.23 ± 6.02 years, 80.21 ± 16.45 kilograms and 179.57 ± 6.93 centimetres respectively. The mean ± SD of the average heart rate in beat per minute and the arterial blood pressure in mmHg before the vestibular stimulation, after the vestibular stimulation in the optimum (+30°) and in the pessimum (-60°) positions and following the last recovery stage following the vestibular stimulation, are shown in Table 1. There were no significant changes in the average heart rate and arterial blood pressure after vestibular stimulation. The side and the position of the vestibular stimulation had also no significant effects on average heart rate and arterial blood pressure.

The mean ± SD of respiratory rate after vestibular stimulation in optimum position was slightly more than the pessimum position in both sides (18.54 ± 2.40 *vs* 17.42 ± 2.45 in the left side and 18.54 ± 2.04 *vs* 17.88 ± 2.74 in the right side), but these differences were not statistically significant (Figure 3).

The mean ± SD of respiratory amplitude after vestibular stimulation in optimum position was slightly less than the pessimum position in both sides (5.82 ± 2.35 *vs* 6.41 ± 3.01 in the left side and 5.86 ± 2.43 *vs* 6.56 ± 3.14 in the right side), but these differences were not statistically significant (Figure 4). For all volunteers, vertigo and the nystagmus of the caloric test had been eliminated at the same 5-min recording stage and before the start of the next recovery phase.

The mean ± SD of the time domain and the frequency domain indices of HRV before vestibular stimulation, after it and following the last recovery stage are summarized in Table 2.

Nystagmus duration of left caloric vestibular stimulations in the optimum and the pessimum positions had significant differences (*e.g.*, 72.14 ± 39.06 *vs* 45.35 ± 35.65, $P < 0.01$). Nystagmus duration of right caloric vestibular stimulations in the optimum and the pessimum positions had also significant differences (*e.g.*, 86.42 ± 67.20 *vs* 50.71 ± 29.73, $P < 0.01$) Figure 5.

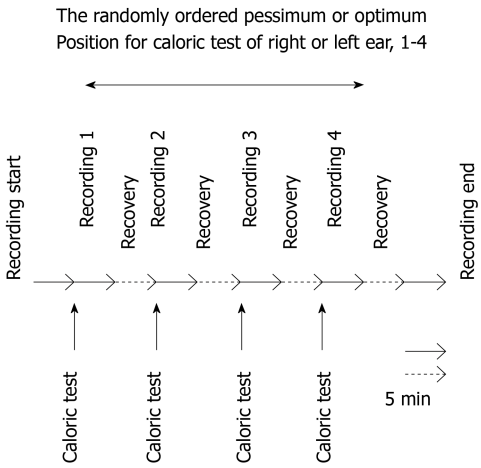

Figure 2 The study design and timeline. Each horizontal arrow is equal to 5 min.

DISCUSSION

These data indicated that despite inducing vestibular stimulation, the 1-s-1-mL ice water caloric test of the right and the left ear had on effect on the short-term HRV indices of cardiac sympathovagal tone in healthy persons. We observed more prolong duration of the nystagmus time in the optimum position. However, the HRV indices had no significant differences following 1-s-1-mL ice water caloric test in the pessimum and the optimum positions. Kasbekar *et al*[39] reported similar results for a standard bi-thermal caloric test. They used 250 mL of 44 ˚C and 30˚C water for caloric stimulation in a fixed order sequence for the right or the left side in all patients. They report no significant changes in heart rate and blood pressure and concluded that the caloric test in stable cardiac patients had no significant effect on hemodynamic parameters[39]. Jauregui-Renaud *et al*[40] reported changes in HRV indices following caloric stimulation. They used 30 ˚C water for caloric stimulation during 120 s and also they used only 2 min periods for calculating the frequency domain indices of HRV and despite these setting, they concluded that the increase in HF power was a manifestation of the effect of the caloric test on respiratory frequency[40]. We also observed a non-significant increase in the respiratory frequency. It occurred during 5 min interval following 1-s caloric test with 1 mL ice water. But we observed that this effect was more prominent in the optimum position than the pessimum position.

The 1-s-1-mL ice water caloric test caused vestibular stimulation as indicated by inducing the nystagmus. This observation was similar to previous reports[34,37]. The caloric test causes vestibular stimulation by indirect and direct mechanisms. The indirect or the main specific mechanism is the endolymph convection and is depended on the head position. The direct or the nonspecific mechanism is due to thermal changes in the activity of vestibular afferents and is independent of the head position. The pessimum position puts the horizontal semi-circular ducts in the horizontal plane and eliminates the effect of gravity on endolymph convection. Therefore, it is used as a type of self-control verification for induction of specific vestibular stimulation; which is only inducible for horizontal semi-circular duct in optimum position. The duration of nystagmus in the optimum position was more than pessimum position in both sides and had significant differences ($P < 0.01$). This finding was expected and indicated a proper vestibular stimulation by the 1-s-1-mL ice water caloric test.

However, the intensity and duration of 1-s-1-mL ice water caloric test were inadequate to elicit a vestibulo-autonomic reflex. The vestibular and the autonomic system may have different sensitivity to caloric stimulation because the vestibular stimulation by 1-s-1-mL ice water caloric test did not provide adequate input for an autonomic output. Many studies reported autonomic effect following vestibular stimulation[18,19,25,27,41] and also many studies reported no autonomic effect following vestibular stimulation[39,42-44]. In addition to adequate vestibular input, the effect size of the vestibulo-autonomic reflex must also set appropriate to show its autonomic laterality. Indeed, many factors can be considered as potential sources of inequality of vestibular effects of caloric stimulation between right and left ears. They are the inter-aural differences in the volume and in the shape of the external ear channels, the variation of co-planarity of semi-circular channels between right and left sides and the laterality in the processing of vestibular inputs *per se*[22,45-48].

Table 1 The mean ± SD of average heart rate and blood pressure (n = 12)

The condition of recording	Average heart rate	Systolic pressure	Diastolic pressure
Before vestibular stimulation	72.33 ± 9.47	123.07 ± 15.41	70.07 ± 6.74
Left vestibular stimulation at +30°	73.41 ± 8.95	127.29 ± 11.68	72.86 ± 5.55
Left vestibular stimulation at -60°	72.16 ± 8.69	127.21 ± 12.03	71.36 ± 7.93
Right vestibular stimulation at +30°	73.13 ± 8.24	128.07 ± 15.42	74.07 ± 6.74
Right vestibular stimulation at -60°	72.13 ± 9.56	126.36 ± 11.15	70.36 ± 7.15
Last recovery stage	70.85 ± 9.10	122.29 ± 11.34	70.64 ± 7.17

The hemispheric dominance of autonomic networks may also cause asymmetric autonomic response following exposure to the one identical stimulus at the right or left side[29-31,49,50].

However, our data did not show any significant differences in short term HRV indices following 1-s-1-mL ice water caloric test on both sides. McGinley *et al*[49] reported lateralization only for sympathetic responses. In the same study, they also used a unilateral facial cooling method for selective increase of parasympathetic tone in one-side and recorded its effect on HRV. They observed no differences between right and left side facial cooling stimulation by this method and concluded that despite prominent lateralization for sympathetic activity, there was no parasympathetic lateralization[49]. We did caloric vestibular stimulation in the pessimum and the optimum conditions and it may cause some degree of simultaneous cervicosympathetic effect. Bolton *et al*[51] reported a very complex interaction among cervical proprioception afferents, respiratory muscles, sympathetic tone and vestibular system in cats. However, there are limited data about cervicosympathetic effect on respiration, heart rate and blood pressure in normal humans[52,53].

Our data may provide further clinical support regarding the cardiovascular safety of the 1-s-1-mL ice water caloric test. There is limited data about the safety of different methods of vestibular assessment including the caloric test in cardiovascular patients[39]. The research implication of this data is introducing a model for studying the concept of the laterality of vestibulo-autonomic reflex. In contrast to microgravity methods or tilt test, the caloric test can provide specific data because it does not cause hemodynamic compensatory responses due to orthostasis. Therefore, adequate vestibular stimulation by irritation with more volume of cold water or in longer duration *e.g.*, more than a few seconds may cause different results.

This study had some limitations and any generalization of data need more caution. They included small sample size, visual monitoring of nystagmus and using fixed level of caloric stimulation. Galvanic vestibular stimulations with increasing intensities, measuring the velocity of different phases of nystagmus by electronystagmography and larger sample size can provide better data about cardiac autonomic laterality of vestibular system.

Table 2 The mean ± SD of the time and the frequency domain indices of heart rate variability (*n* = 12)

	Before vestibular stimulation	Left vestibular stimulation		Right vestibular stimulation		Last recovery stage
		at +30˚	at -60˚	at +30˚	at -60˚	
Total power (ms²)	2009.5 ± 147.9	2905.6 ± 2506.5	8698.7 ± 2185.8	2277.4 ± 1556.3	5063.2 ± 4842.9	3173.9 ± 2562.7
HF ms²	628.25 ± 592.3	871.51 ± 819.6	2472.36 ± 629.6	527.50 ± 415.7	1493.71 ± 1900.2	848.51 ± 862.5
nHF (nu)	47.63 ± 19.35	42.76 ± 12.34	40.25 ± 12.96	40.59 ± 14.81	40.56 ± 10.08	40.15 ± 13.76
LF ms²	434.94 ± 320.27	697.00 ± 554.68	2048.37 ± 479.73	581.52 ± 551.35	1015.51 ± 905.88	753.21 ± 457.60
nLF (nu)	44.85 ± 18.78	45.31 ± 17.48	46.85 ± 17.52	50.57 ± 17.97	43.09 ± 17.83	49.76 ± 18.71
LF/HF	1.33 ± 1.07	1.34 ± 1.21	1.32 ± 0.7	1.57 ± 1.05	1.18 ± 0.71	1.61 ± 1.38
SDNN (ms)	44.85 ± 17.85	56.55 ± 26.06	70.95 ± 63.38	50.12 ± 16.48	61.24 ± 25.08	55.63 ± 18.84
SD delta NN (ms)	36.00 ± 20.42	48.76 ± 34.26	67.81 ± 81.36	40.04 ± 17.64	58.44 ± 40.01	49.45 ± 29.70
SDNN/SD delta NN	1.429 ± 0.468	1.421 ± 0.561	1.359 ± 0.525	1.385 ± 0.388	1.318 ± 0.548	1.321 ± 0.441
RMSSD	35.95 ± 20.39	48.70 ± 34.22	67.69 ± 81.18	39.98 ± 17.61	58.36 ± 39.96	49.37 ± 29.63
Maximum NN (ms)	988.5 ± 158.4	1085.5 ± 273.35	1197.6 ± 352.8	1033.6 ± 193.9	1267.6 ± 384.1	1122.2 ± 232.8
Minimum NN (ms)	704.30 ± 82.52	687.78 ± 72.81	685.34 ± 104.34	685.00 ± 59.56	690.15 ± 119.1	695.47 ± 85.85
Range NN (ms)	284.2 ± 113.7	397.8 ± 279.8	511.7 ± 380.1	348.6 ± 159.1	577.4 ± 404.4	426.7 ± 248.7
Mean NN (ms)	843.2 ± 113.6	829.2 ± 106.0	844.0 ± 113.9	829.9 ± 90.9	846.2 ± 119.0	860.2 ± 114.0
Normals (%)	99.13 ± 1.34	99.41 ± 1.07	98.93 ± 1.56	99.43 ± 0.96	98.54 ± 2.29	98.10 ± 3.86
Ectopics (%)	0.87 ± 1.34	0.56 ± 0.99	1.07 ± 1.56	0.57 ± 0.96	1.43 ± 2.27	1.88 ± 3.86

VLF: Very-low-frequency; LF: Low-frequency; HF: High-frequency; nLF: Normalized value of LF; nHF: Normalized value of HF; NN: Beat-to-beat intervals of normal sinus rhythm; SDNN: Standard deviation of NN intervals; SD delta NN: Standard deviation of the differences between adjacent NN intervals; RMSSD: Square root of the mean of the squares of the successive differences between adjacent NNs.

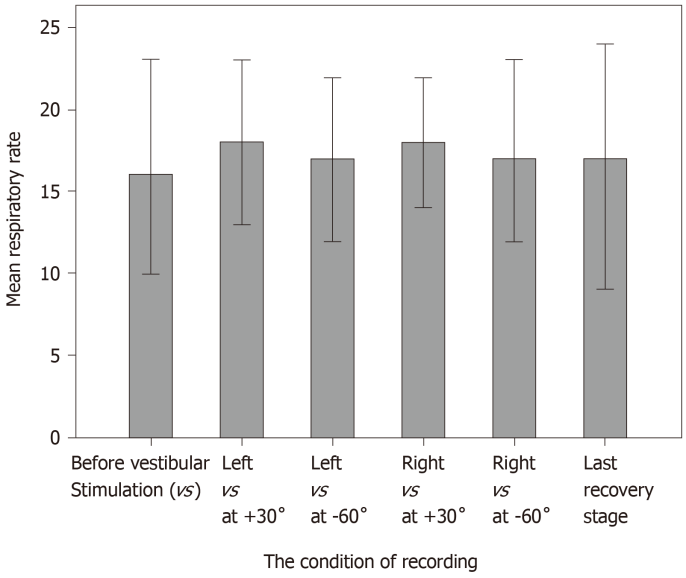

Figure 3 The mean ± SD of respiratory rate before vestibular stimulation, after it and following the last recovery stage (*n* = 12).

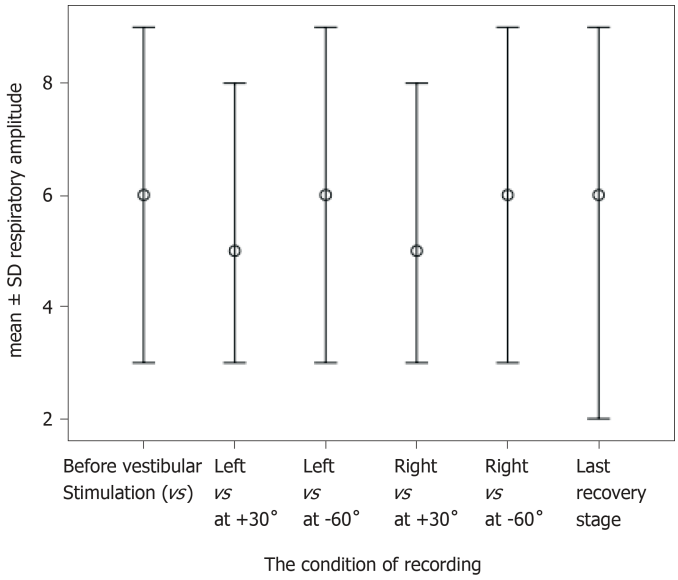

Figure 4 The mean ± SD of respiratory amplitude before vestibular stimulation, after it and following the last recovery stage (*n* = 12).

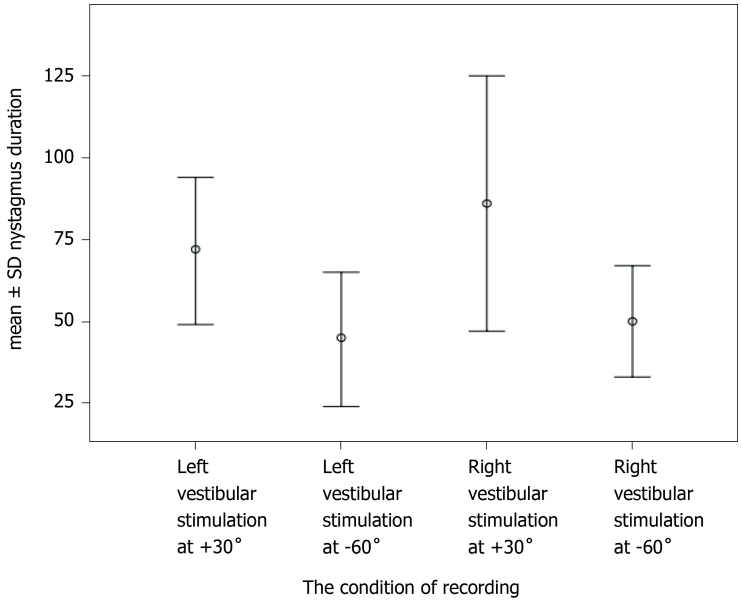

Figure 5 The mean ± SD of nystagmus duration in seconds after caloric vestibular stimulation of each ear in the optimum (+30º) and in the pessimum (+60º) conditions (*n* = 12).

ARTICLE HIGHLIGHTS

Research background

The caloric vestibular stimulation provides the opportunity for isolated and unilateral activation of the vestibular system. Therefore, it may be very helpful as a model for comparison of the effect of vestibulo-autonomic reflex on cardiovascular system and for exploration of differences between the right and the left sides.

Research motivation

There is very limited information about the autonomic laterality. The autonomic effects of vestibular system are well documented but the reports about the laterality of vestibular effect on cardiovascular system is rare.

Research objectives

To compare the effect of the caloric test on the cardiac sympathovagal tone and to study any difference between the autonomic effects of the right and the left side caloric vestibular stimulations.

Research methods
This self-control study was conducted on 12 healthy male volunteers. The minimal ice water caloric test was applied for vestibular stimulation in the optimum and in the pessimum positions for each side. The time domain and the frequency domain indices of the heart rate variability were used as markers of cardiac sympathovagal tone.

Research results
Caloric test induced nystagmus and vestibular stimulation in the optimum positions but had no effect on blood pressure, average heart rate and heart rate variability.

Research conclusions
The minimal ice water caloric test was well tolerable, provided inadequate vestibular autonomic stimulation and may have introduced a model for studying the concept of the laterality of vestibulo-autonomic reflex.

Research perspectives
The vestibular and the autonomic system may have different sensitivity to caloric stimulation and the irritation with more volume of cold water or in longer duration *e.g.*, more than a few seconds may cause adequate autonomic vestibular stimulation.

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CASE REPORT

Subclavian Impella 5.0 to the rescue in a non-ST elevation myocardial infarction patient requiring unprotected left main rotablation: A case report

Vasileios Panoulas, María Monteagudo-Vela, Konstantinos Kalogeras, Andre Simon

ORCID number: Vasileios Panoulas (0000-0002-9894-9200); María Monteagudo-Vela (0000-0002-2086-8718); Konstantinos Kalogeras (0000-0003-2036-6192); Andre Simon (0000-0001-7686-5252).

Author contributions: Panoulas V drafted the manuscript; Panoulas V, Monteagudo-Vela M and Kalogeras K performed the case and collected the images; Simon A reviewed the manuscript and offered clinical advice.

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Vasileios Panoulas, Konstantinos Kalogeras, Department of Cardiology, Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust, London UB9 6JH, United Kingdom

Vasileios Panoulas, Cardiovascular Sciences, National Heart and Lung Institute, Imperial College, London SW7 2BU, United Kingdom

María Monteagudo-Vela, Andre Simon, Department of Cardiothoracic Transplantation and Mechanical Circulatory Support, Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust, London UB9 6JH, United Kingdom

Corresponding author: Vasileios Panoulas, MD, MRCP, PhD, Honorary Senior Lecturer at Imperial College London, Consultant Cardiologist, Department of Cardiology, Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust, Hill End Road, Harefield, London UB9 6JH, United Kingdom. v.panoulas@imperial.ac.uk

Abstract

BACKGROUND

Often in patients with significant three-vessel or left main disease there is coexistent significant peripheral disease rendering them poor candidates for percutaneous left ventricular support during revascularization. Evidence on the management of such cases is limited.

CASE SUMMARY

We describe a case of such a patient with critical distal left main disease and chronically occluded right coronary artery who presented with chest pain and a non-ST elevation myocardial infarction and had significantly impaired left ventricular function. With the aid of our cardiothoracic surgeons a cut down subclavian Impella 5.0 was inserted and high risk rotablation percutaneous coronary intervention carried out successfully.

CONCLUSION

This case highlights the need for cross-specialty collaborations in such high-risk cases were alternative access is needed for insertion of large bore mechanical circulatory support devices.

Key words: Impella; Subclavian; Rotablation; Left main; Percutaneous coronary intervention; Case report

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Core tip: This case highlights the importance of the coming together of the cardiothoracic surgeons and interventional cardiologists in treating patients in caridogenic shock with high risk coronary anatomy features. In this particular case the Impella 5.0 was implanted using a surgical cut down through the subclavian access and supported extreme high risk unprotected left main rotablation percutaneous coronary intervention. The patient made an excellent recovery with remarkable left ventricular function improvement in one-year follow-up.

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INTRODUCTION

In patients with stable coronary disease, the use of Impella for high risk percutaneous coronary intervention (PCI) has been associated with improved mid-term outcomes compared to intra-aortic balloon pump[1,2]. Data from the large retrospective evaluation of the USpella registry[3] support the feasibility, safety, and hemodynamic usefulness of Impella device for the treatment of unprotected left main interventions using the percutaneous 2.5 and CP Impellas. However, often in these high-risk patients, the iliofemoral disease is so extensive that does not allow percutaneous peripheral arterial interventions. Limited reports exist on the management of such patients that require alternative access for mechanical circulatory support.

CASE PRESENTATION

We present a case of a well-functioning 71-year-old gentleman who was originally admitted with chest pain via the primary PCI pathway.

On admission he had a blood pressure of 145/85 mmHg with regular pulse and a soft ejection systolic murmur. His lung auscultation revealed bibasal crepitations and he had pitting oedema to his mid shins. He was saturating on air at 94%.

His electrocardiogram showed transient anteroseptal ST elevation and a small troponin rise of 400 ng/L.

His left ventricular (LV) function was severely impaired with ejection fraction of 30%, inferior partial scar and hypokinesia elsewhere. He also had mild aortic stenosis.

He had extensive peripheral arterial disease (PAD) with external iliac diameters of 3.5 mm bilaterally, previous aortic stent, endovascular aneurysm repair for abdominal aortic aneurysm (Figure 1A), right carotid endarterectomy, old right basal ganglia ischaemic infarct, hypertension, hypercholesterolaemia and smoking.

FINAL DIAGNOSIS

Coronary angiogram performed immediately on admission (Figure 1B) showed a tight calcific distal left main stem (LMS) bifurcation, tight proximal calcific left circumflex and significant calcific mid left anterior descending lesions. Right coronary artery was chronically occluded proximally and collateralized by the left system. By the end of the diagnostic procedure his chest pain had settled and the patient was discussed with the on-call surgeon.

In essence this patient presented with a non-ST elevation myocardial infarction with critical distal calcific left main disease, which was his last remaining conduit as his right coronary artery was a chronic total occlusion.

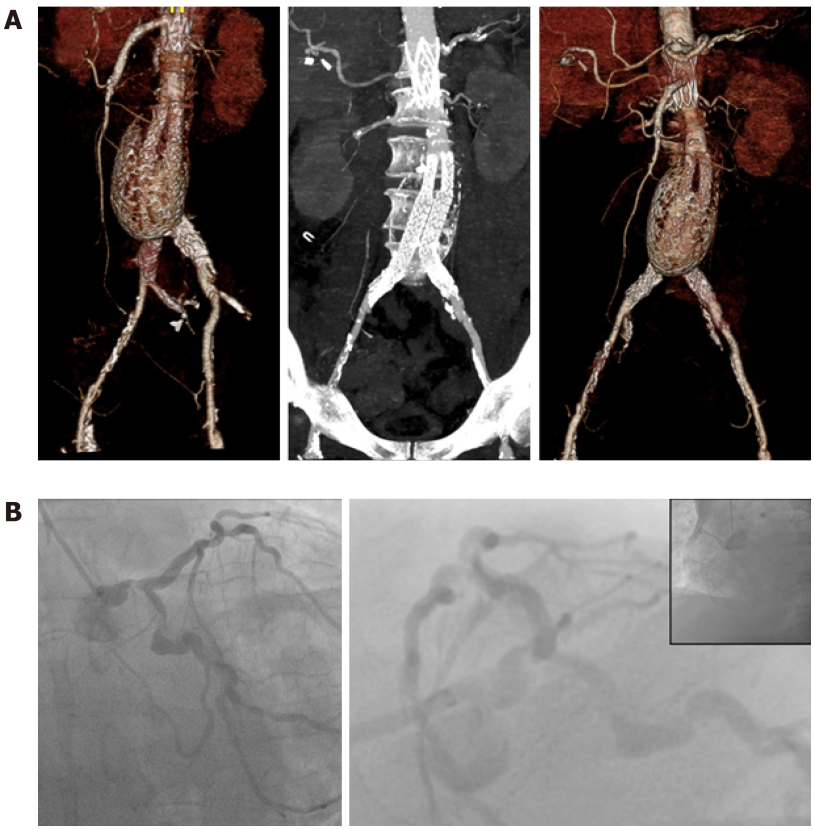

Figure 1 Heavily diseased peripheral and coronary vascular trees. A: 3D reconstructions of abdominal and ilio-femoral arterial systems showing previous abdominal aneurysm, and endovascular aneurysm repair alongside the extensive ilio-femoral disease; B: Initial coronary angiogram demonstrating tight distal left main stem and proximal left circumflex calcific disease. The right coronary artery is a chronic total occlusion.

TREATMENT

The heart team agreed on urgent coronary artery bypass grafting. However, over the next couple of days, while completing his pre-surgical work-up (including carotid doppers, deptartmental echocardiogram and lung function tests), he developed recurrent transient STE chest pains with troponin rise up to 7000 ng/L, pulmonary oedema and impending cardiogenic shock with LV deterioration to 15%.

At that stage, an urgent decision was made by the heart team for high-risk PCI using Impella 5.0 support *via* the subclavian access, under general anaesthesia. The subclavian artery was dissected and exposed. A 10-mm silver-coated Dacron graft was anastomosed to the subclavian artery and a 5.0 Impella was placed successfully in the LV (Figure 2).

Subsequently using the right femoral access and an 8F EBU 3.5 guidecather the left main was initially rotablated with 1.75 mm burr. The loss of pulsatility during the runs was prominent, however mean arterial pressure was sustained at about 55 mmHg due to the presence of the 5.0 Impella (Figure 3). Despite a couple of complications and equipment failures, including localized LMS dissection balloon entrapment on coronary wire and undeployed stent dislodgement, a good result was obtained with reverse culotte LMS bifurcation stenting and targeted PCI of mid left anterior descending and proximal left circumflex lesions (Figure 4).

OUTCOME AND FOLLOW-UP

Following his successful LMS bifurcation rotablation PCI the patients was extubated the following day and the Impella 5.0 explanted 5 d later. He made an excellent recovery and was discharged home 10 d later. On one-year follow up the patient was doing remarkably well and his LV had recovered fully, with a current ejection fraction of 55%. He is fully compliant with his heart failure and antiplatelet regime. He still has mild aortic stenosis for which he will be kept under surveillance on an annual basis.

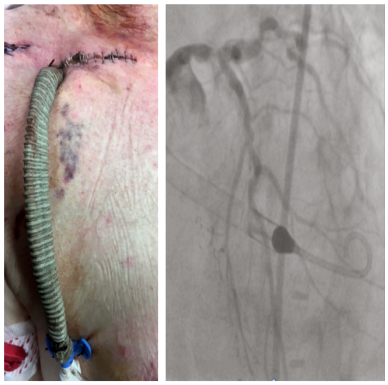

Figure 2 A 10-mm silver-coated Dacron graft was anastomosed to the subclavian artery and an Impella 5.0 was inserted.

DISCUSSION

This case illustrates the importance of cross-specialty collaboration in overcoming challenges in coronary revascularization of high-risk patients with prohibited iliofemoral access for percutaneous mechanical circulatory support devices.

The co-existence of PAD and cardiovascular disease (CVD) is common with nearly 45% of patients with PAD suffering from simultaneous cardiovascular disease[4]. Recently the first use of intravascular lithotripsy (IVL) to treat vascular disease using the Shockwave IVL device (Shockwave Medical Inc) in iliofemoral arteries for modification of calcified plaque in an attempt to facilitate percutaneous Impella CP implantation was described[5]. Furthermore a fully percutaneous transaxillary approach for implantation of Impella CP was been described and is feasible[6,7]. When it comes, however, to implantation of an Impella 5.0 percutaneous options are limited (*e.g.* transcaval[8]), whereas surgical axillary cut-down has been established as a safe technique[9].

An alternative approach to tackling this case may have been the use of Impella 5.0 to stabilize the patient prior to off-pump CABG. However, our surgical team felt that in view of the ongoing ischaemic symptoms, the surgical risk would have been prohibitive and an immediate treatment with PCI would be the preferred option.

CONCLUSION

Our case report suggests that the use of surgical cut down to facilitate last remaining conduit high risk PCI in unstable patients with poor left ventricular function is feasible and safe. (1) Impella 5.0 provides a high level of support, which allows the operators to optimize their revascularization techniques and overcome, without stress, complications that may occur during high risk left main PCI (last conduit); (2) The Impella 5.0 can be inserted using subclavian cut down in cases with peripheral vascular access not amenable to large bore access. The transcaval access technique, even though promising for Impella 5.0, has yet to be widely adopted; and (3) Despite the emergence of IVL often in patients with very extensive disease IVL and peripheral angioplasty may not be feasible and a cross-specialty collaboration is needed to facilitate use of alternative access for mechanical circulatory support.

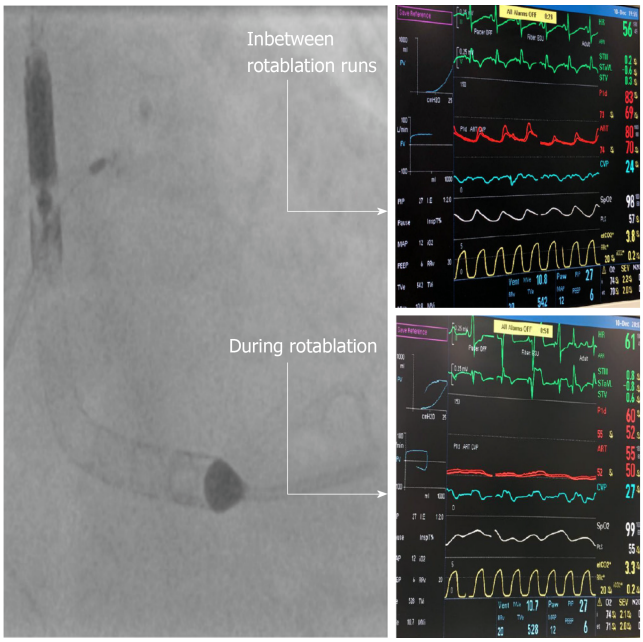

Figure 3 During rotablation runs with the 1.75 mm burr the pulsatility was lost, however, the mean arterial pressure was maintained due to the presence of the Impella.

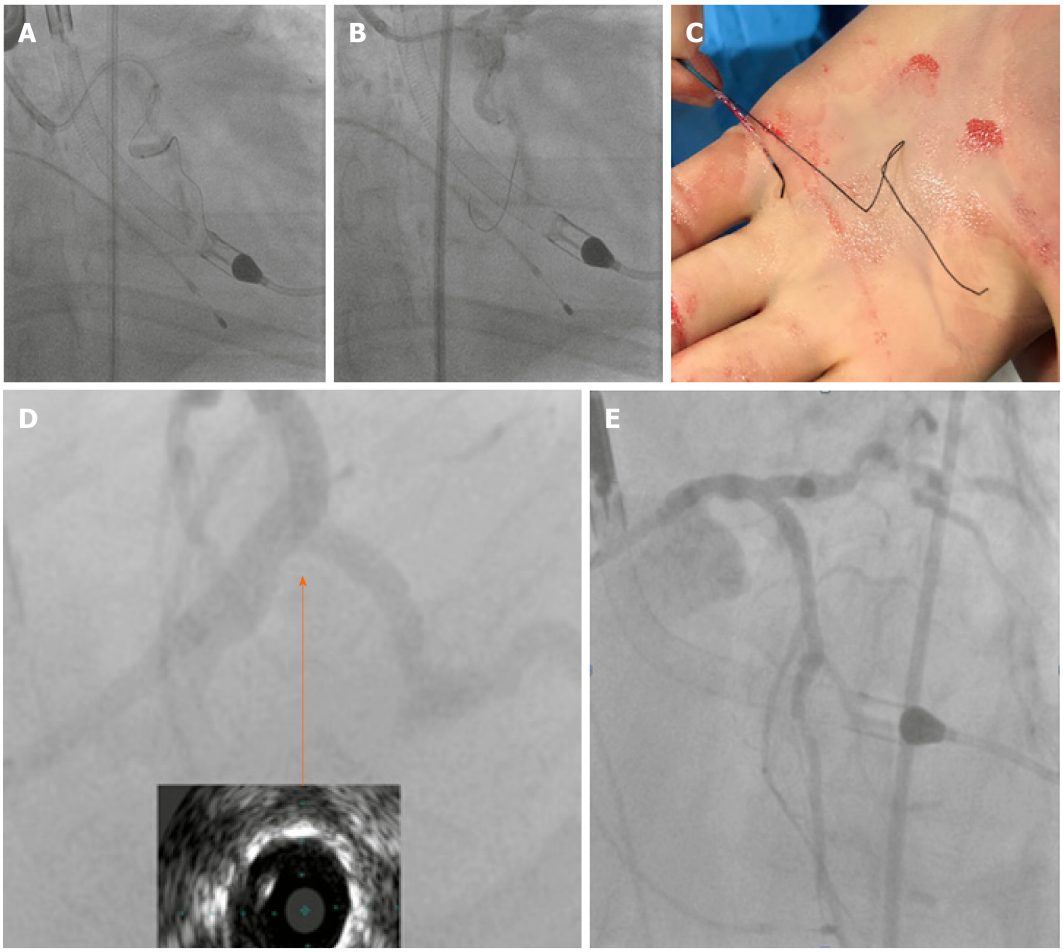

Figure 4 After a stormy procedure a good angiographic and intravenous ultrasound result was obtained. A: Support issues despite use of guideliner leading on to stent dismounting off its balloon undeployed after it got trapped on a calcific bend; B: Localised small perforation/dissection at the distal left main; C: Extreme left circumflex tortuosity causing deformation of Choice PT XS coronary wire and balloon trapping on the wire; D: Spider view and intravenous ultrasound in distal left main stem showing good stent expansion and apposition; E: LAO cranial view showing good final left main stem Culotte result.

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