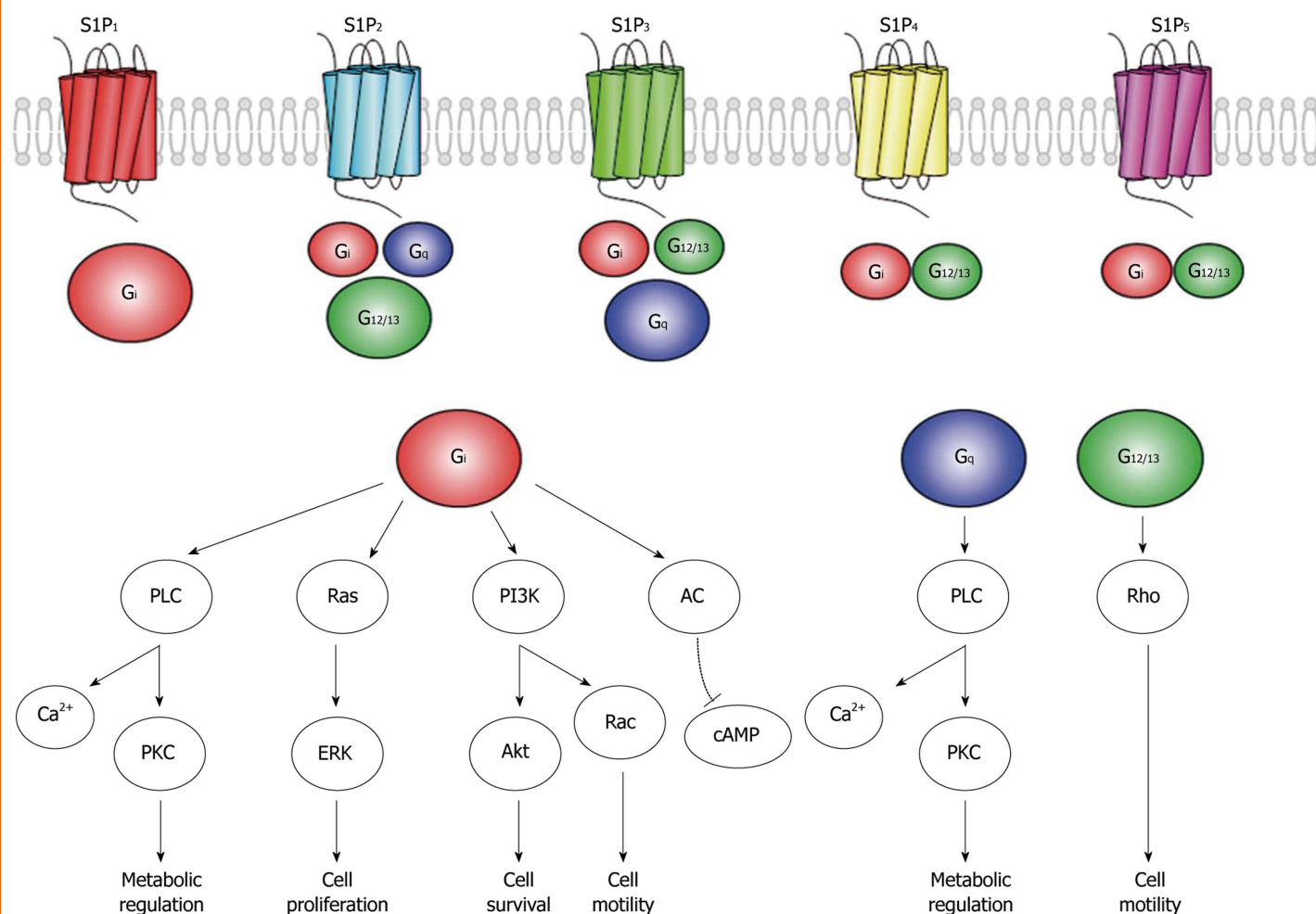


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## From the epicardial adipose tissue to vulnerable coronary plaques

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most common underlying substrate in patients suffering acute coronary thrombotic events. Recently, an interesting association between TCFAs and a particular depot of visceral fat called epicardial adipose tissue has been suggested. In this study, we review some basic and clinical aspects of behind this interesting association as well as the value of optical coherence tomography in the diagnosis of TCFAs.

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### Abstract

Thin cap fibroatheromas (TCFAs) are thought to be the most common underlying substrate in patients suffering acute coronary thrombotic events. Recently, an interesting association between TCFAs and a particular depot of visceral fat called epicardial adipose tissue (EAT) has been suggested. In this article, we discuss some basic and clinical aspects of this association and then briefly review some of the pathophysiological characteristics attributed to EAT that explain why this particular depot of fat has been attracting the attention of the cardiological scientific community in recent years. Finally we discuss the value of optical coherence tomography in the diagnosis of TCFAs and the role of multislice computed tomography to assess EAT.

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**Key words:** Epicardial adipose tissue; Thin-cap fibroatheromas; Coronary thrombotic events; Optical coherence tomography; Multislice computed tomography

**Core tip:** Thin cap fibroatheromas (TCFAs) are the

### SEARCH FOR THE "GUILTY" SUBSTRATE BEHIND CORONARY THROMBOTIC EVENTS

Despite widespread adoption of preventive measures and remarkable improvements in medical treatment and revascularization strategies for patients with coronary artery disease (CAD), atherosclerosis and its thrombotic complications continue to be the most deadly and disabling disease in industrialized countries<sup>[1]</sup>. As cardiologists, we have struggled for decades in accurately identifying individuals that despite being asymptomatic have a high individual risk of developing thrombotic coronary events. Accordingly, the identification of the so-called "vulnerable" or "high risk plaque" in the coronary tree has been one of the main challenges and pivotal areas of research in modern cardiovascular medicine.

Combined evidence provided by autopsy as well as from invasive studies has shown that rupture-prone plaques have certain characteristics: a thin fibrous cap, a large lipid-rich pool and increased macrophage activity (Figure 1)<sup>[2-5]</sup>. Currently, there is sound evidence suggest-

ing that these plaques, namely “thin cap fibroatheromas” (TCFAs), are the most common underlying “guilty” substrate in patients suffering acute coronary thrombotic events<sup>[3,6]</sup>. Moreover, an in-depth analysis of the PROSPECT trial demonstrated that, in spite of significant efforts in secondary prevention, TCFAs remain powerful independent predictors of recurrent adverse cardiovascular events<sup>[7]</sup>.

Considering this pathological and clinical background, great efforts have been made in order to identify TCFAs with the ultimate goal of preventing plaque rupture and thereby averting acute coronary syndromes and sudden cardiac death. However, the correct diagnosis of these vulnerable plaques by non-invasive imaging techniques (potentially available and suitable in large patient populations) remains a challenge<sup>[8]</sup>. Therefore, new diagnostic clues aiming to the identification of these vulnerable plaques, are always received with major enthusiasm by the scientific community. On these grounds, the recently reported association between coronary TCFAs and a specific, readily-accessible, depot of visceral fat called “epicardial adipose tissue” (EAT) (Figure 2) reported by Ito *et al.*<sup>[9]</sup> deserves to be highlighted as a valuable step-forward in the right direction.

## EPICARDIAL ADIPOSE TISSUE AND THIN CAP FIBROATHEROMAS: A RECENTLY SUGGESTED ASSOCIATION

Very recently, Ito *et al.*<sup>[9]</sup> reported for the first time the relationship between EAT, as quantified with multislice computed tomography (MSCT), and plaque vulnerability, as assessed with intracoronary optical coherence tomography (OCT). This is of remarkable importance because at this moment and notwithstanding well-recognized limitations, MSCT and OCT are the “gold standards” for assessing EAT and plaque vulnerability *in vivo*, respectively (Figure 3). In their study, Ito *et al.* made a profound examination of a total of 180 vessels from 117 patients with stable angina or acute coronary syndromes that underwent OCT during cardiac catheterization and also a MSCT study within an interval of  $9.8 \pm 8.8$  d. TCFAs were assessed with OCT and defined as plaques with necrotic lipid pools  $\geq 2$  quadrants and minimum fibrous cap thickness measuring  $< 65 \mu\text{m}$ . EAT, coronary plaques, coronary plaques attenuation and the remodeling index which are MSCT findings associated with plaque vulnerability<sup>[10,11]</sup> were evaluated from MSCT images. Notably, both of these techniques were performed following a rigorous methodology, as demonstrated by their very low inter and intraobserver variability. After categorizing the patients according to EAT tertiles, they found that all of the aforementioned indexes of plaque vulnerability provided by OCT and MSCT, were higher in those within the highest tertile of EAT (high-EAT). Moreover, EAT was significantly correlated with the extension of the necrotic lipid pool and inversely correlated with the

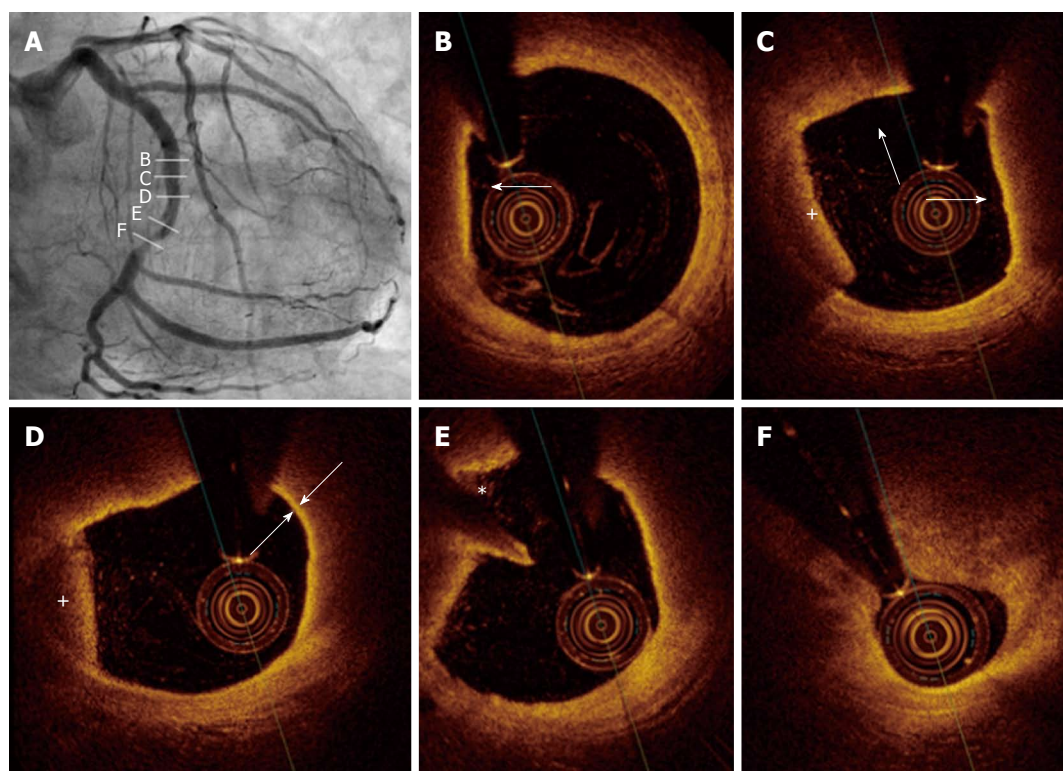
thickness of the fibrous cap by OCT ( $r = -0.400$ ,  $P < 0.01$ ). Finally, high-EAT was an independent predictor of TCFAs [RR, 2.92 (1.13-7.55)] and of acute coronary syndromes as a clinical presentation [RR, 2.89 (1.14-7.29)].

Therefore, the authors have provided for the first time strong evidence *in vivo* linking EAT with the vulnerable or high-risk plaques behind coronary thrombotic events and unstable clinical presentations. The authors are to be congratulated on executing this cleverly designed study although a few minor limitations and future challenges are nonetheless worth noting. First, as in all cross sectional studies, causality cannot be assumed and, therefore, these findings should be taken as hypothesis generating and confirmed by prospective studies. Second, the relatively small sample size could be a limitation when drawing conclusions. Third, all of the patients included in the study had already symptoms of CAD so the translation of these findings to an asymptomatic population in terms of primary prevention is unclear. Finally, OCT and MSCT have well-acknowledged limitations in identifying plaque vulnerability and TCFAs but by far, are the best available tools for this purpose *in vivo*<sup>[3,6,10,11]</sup>. This study is also an excellent opportunity to briefly review some basic and clinical characteristics attributed to EAT that explains why this particular adipose tissue has been attracting the physician's attention in the recent years.

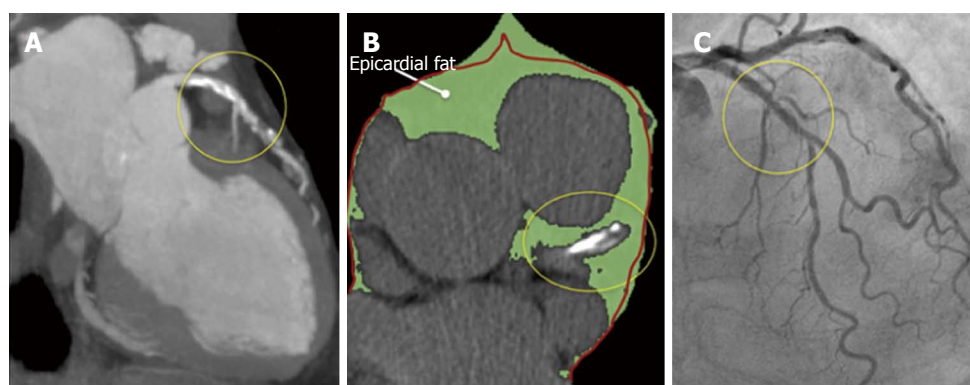
## ANATOMY AND PHYSIOLOGY OF EPICARDIAL ADIPOSE TISSUE

EAT is an intrathoracic depot of visceral fat that lays over the myocardium and coronary arteries that has received increased attention in the literature in recent years, due to some unique and very interesting characteristics. Embryologically, EAT originates from the splanchnopleuric mesoderm and evolves from brown adipose tissue<sup>[12]</sup>. In the normal human heart, EAT follows the adventitia of coronary arteries, is concentrated in the atrioventricular and interventricular grooves and represents approximately 20% of the heart mass<sup>[13]</sup>. Remarkably, no structures resembling a fascia (as found on skeletal muscle) separates EAT from the myocardium and coronary vessels and therefore these three tissues share the same circulation and innervation<sup>[14]</sup>. Because of this anatomical contiguity, it was proposed that EAT could interact locally with the myocardium and coronary arteries through paracrine or vasocrine pathways and a growing amount of evidence is currently supporting this assumption<sup>[15]</sup>.

Besides its embryology and anatomy, the physiology of EAT is also quite special and important differences have been shown in its metabolism when compared with other depots of corporal fat. For example, a higher rate of lipolysis and insulin-induced lipogenesis has been observed in EAT from animal models<sup>[12]</sup>. Human EAT appears to be richer in saturated fatty acids than subcutaneous fat and, interestingly, the rates of free fatty acids synthesis, incorporation and breakdown are significantly



**Figure 1** A 64-year-old male was admitted at our hospital because of progressive angina. A: Coronary angiogram demonstrated a complex stenosis in the mid segment of the circumflex coronary artery; B-F: Optical coherence tomography revealed a large complex thin-cap fibroatheroma (arrows) proximal and at the site of the stenosis. The fibrous cap covering the lipid rich plaque had a variable thickness and in its thinnest part measured 55  $\mu\text{m}$  (arrows in D). Distally, the same plaque had large lipidic core and an image compatible with a rupture site (\*) (E). Please note that residual lining red thrombus with a clear dorsal shadowing was also detected at some sites (+). Finally, at the most severe site (F), a fibrous plaque was noted.

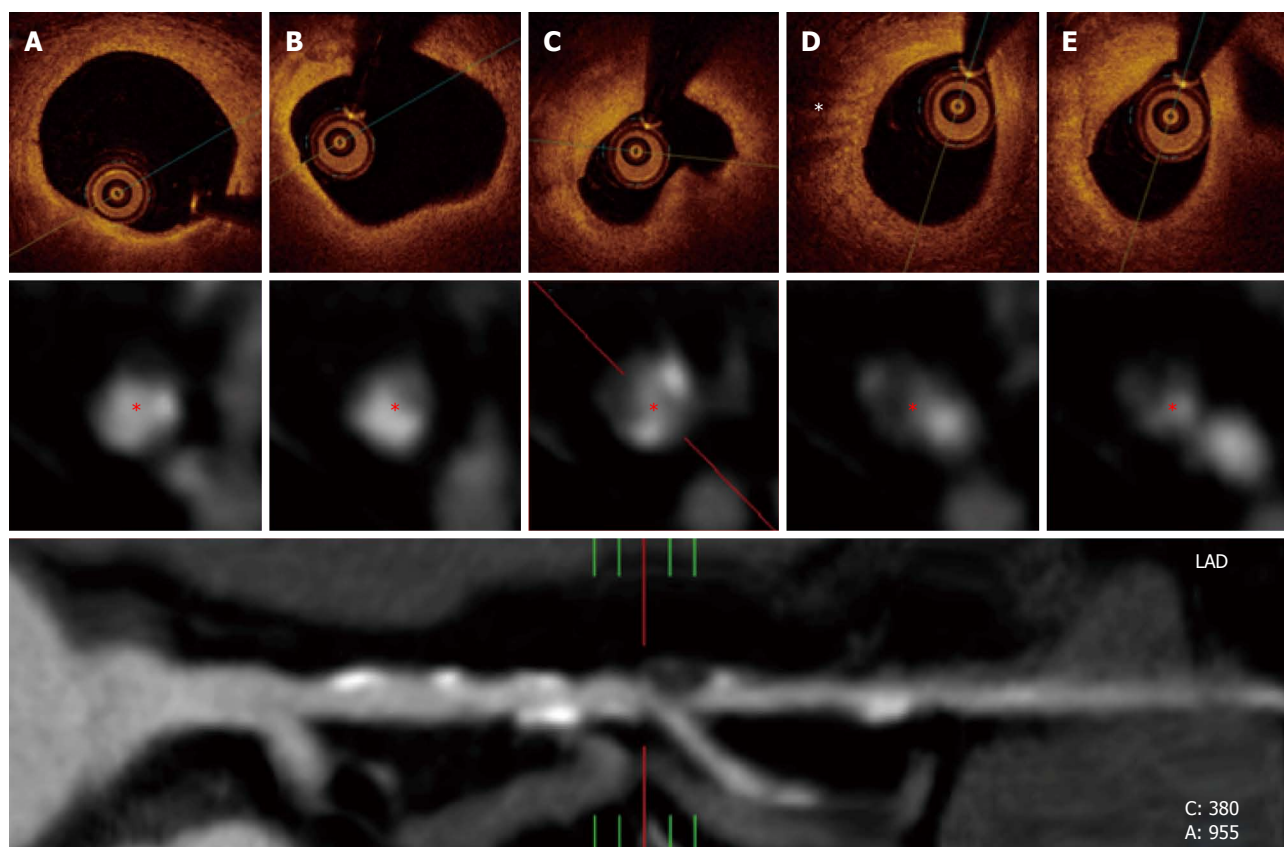


**Figure 2** A multislice computed tomography was performed in a 68-year old male because of atypical chest pain. A: This study revealed a long mixed, calcific and non-calcific plaque in the proximal and mid segments of the left anterior descending artery; B: A large amount of epicardial adipose tissue (EAT) [(159.2  $\text{cm}^3$  (figure 3)] was also calculated. Please note that the left anterior descending artery is embedded in EAT (yellow circles). The red line represents the pericardium; C: A coronary angiogram was scheduled and revealed intermediate stenoses in the same arterial segment that was subsequently studied with optical coherence tomography.

higher in EAT<sup>[12,16]</sup>. Since 50%-70% of the energy requirements of the heart are supplied by free fatty acids oxidation, it has been proposed that EAT might provide large amounts of energy to the myocardium under non ischemic conditions<sup>[15]</sup>. Besides its role in the energetic metabolism, other physiological functions of EAT have been proposed. Indeed, EAT may be a source of anti-atherogenic and anti-inflammatory adipokines, such as adiponectin and adrenomedullin, may influence vasomo-

tion of coronary arteries and may also provide mechanical and thermogenic cardioprotection to the myocardium and coronary arteries by attenuation of vascular tension and torsion<sup>[15,17,18]</sup>.

Altogether, current evidence supports the hypothesis that under physiological conditions, EAT supplies energy and heat to the coronary arteries and myocardium and may also exert a protective modulation on the coronary vessels<sup>[15,17,19]</sup>. However, as will be discussed in the next



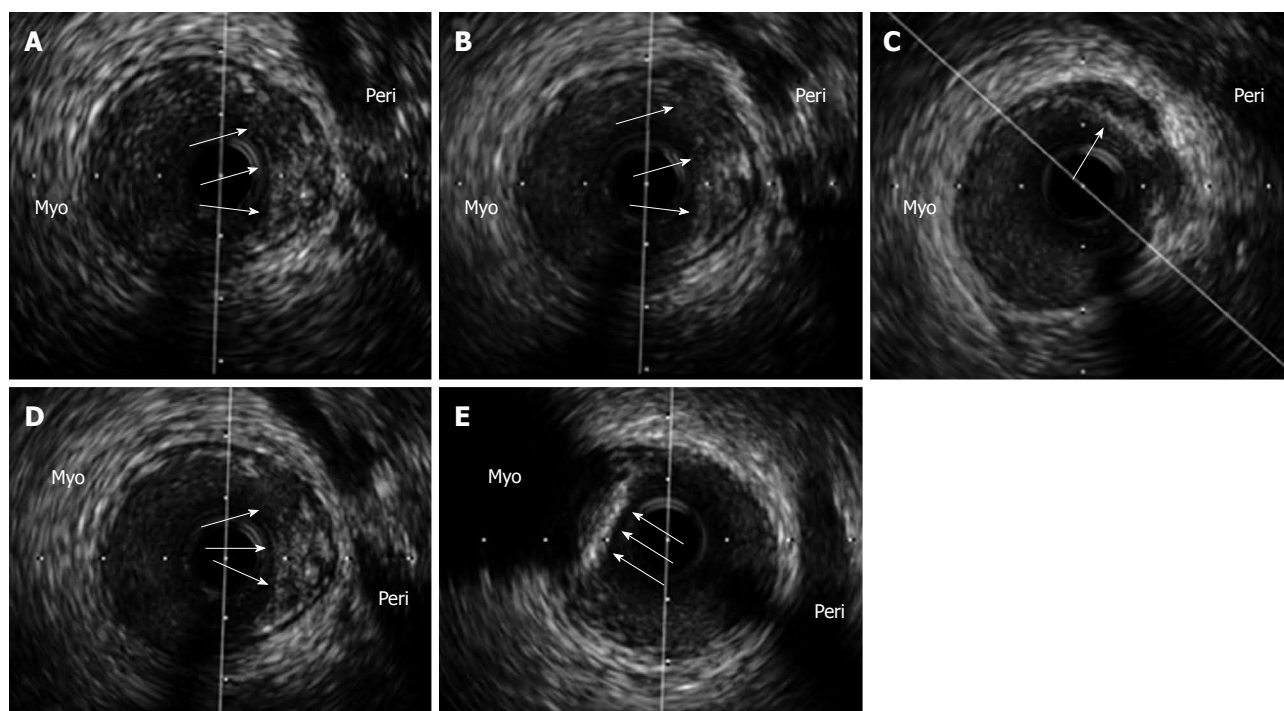
**Figure 3** Optical coherence tomography and multislice computed tomography findings of the same patient in figure 2. A and B: In the upper panel, optical coherence tomography revealed a complex plaque affecting a long portion of the vessel with calcified and lipidic regions; C: Also, a complex fibroatheroma that included a lipidic core was observed at the site of the most severe stenosis; D: A high light attenuation band with distal shadowing can be attributed to macrophage infiltration (\*). The middle panel represents cross-sectional views of the vessel at the same stenosis as visualized by multislice computed tomography (MSCT). Calcified and non-calcified regions including eccentric plaques were found within the diseased segment. The inferior panel shows a MSCT multiplanar reconstruction of the vessel and its anatomical bookmarks.

paragraph, a growing body of evidence is associating EAT with pathological states from which atherosclerotic plaque development and instability are of substantial importance.

## EPICARDIAL ADIPOSE TISSUE AND ITS IMPACT ON THE DEVELOPMENT OF ATHEROSCLEROTIC PLAQUES

From a clinical perspective, several clinical and epidemiological studies have associated EAT with different cardiometabolic risk factors and with early stages of atherosclerosis and plaque formation<sup>[20-24]</sup>. Moreover, the presence and severity of CAD and coronary calcification, indicating more advanced states of atherosclerosis, have been also associated with EAT<sup>[25-28]</sup>. This association has been reinforced by a recent meta-analysis ( $n = 2872$  patients) that found that when compared with patients without CAD, EAT thickness and volume were significantly higher in those with documented CAD<sup>[29]</sup>. These epidemiological findings have been supported by a large amount of basic evidence pointing at the same

direction. Indeed, when compared to subcutaneous fat, EAT shows a more dense inflammatory cell infiltrate, predominantly represented by macrophages<sup>[30]</sup>. The secretion of some highly atherogenic and inflammatory adipokines such as tumor necrosis factor alpha (TNF- $\alpha$ ), monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), IL-1b, plasminogen activator inhibitor-1 (PAI-1) and resistin are significantly higher in EAT from patients with CAD<sup>[18,31-35]</sup>. Interestingly, another supporting evidence comes from a “natural experiment”, since as shown by animal and human studies, increased atherosclerosis is observed in the segments of the coronary arteries proximal to myocardial bridges, where EAT is present, whereas intramyocardial segments of the vessels are free of atherosclerosis<sup>[36-38]</sup>. Altogether, current evidence supports the hypothesis that under pathological conditions, EAT may become an adverse lipotoxic and proinflammatory organ that could play a significant role in the development of coronary atherosclerosis. Notably, however, it was not until very recently that EAT was linked with different characteristics of coronary atherosclerotic plaques and more importantly, plaque vulnerability.



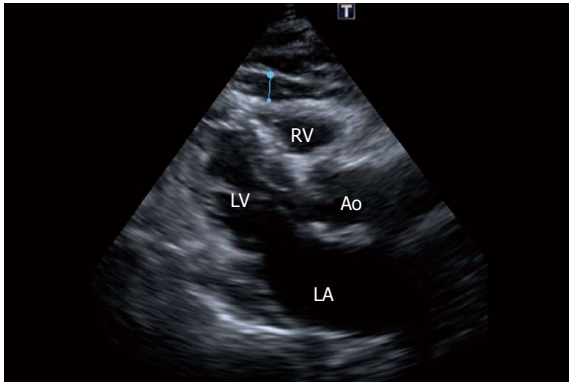
**Figure 4** An intravascular ultrasound analysis of the left anterior descending coronary artery in an asymptomatic patient with a previously deployed stent (not shown) that underwent this study as part of an institutional protocol. A-D: In the pericardial side (Peri) of the vessel, an eccentric and positively remodeled plaque with heterogenic echo-reflection that included a hypoechoic area, suggestive of a potentially "high risk" plaque, was found (arrows); E: Interestingly, just adjacently and in the opposite vessel side [myocardial side (Myo)], a calcified plaque with intense posterior shadowing, highly suggestive of a stable fibro-calcific plaque (arrows), was also observed. The patient has been asymptomatic during a 3-year clinical follow-up.

## EPICARDIAL ADIPOSE TISSUE AND PLAQUE VULNERABILITY

Although the precise mechanisms of plaque rupture are poorly understood, it is widely accepted that the disruption occurs at the site of the fibrous cap, which is usually thin, heavily infiltrated by macrophages and T-lymphocytes and where the underlying necrotic core is also typically large<sup>[2]</sup>. Various factors and hypothesis have been implicated and proposed in order to explain these phenomena. These include arterial remodeling<sup>[39,40]</sup>, inflammation and apoptosis within the plaque<sup>[41,42]</sup>, impaired collagen synthesis and breakdown in the fibrous cap<sup>[43]</sup> and local mechanical stress<sup>[44]</sup>. EAT, interestingly, appears to be related to some of these. For example, some adipokines highly expressed by EAT, such as TNF- $\alpha$ , IL-1 and MCP-1, have been associated with macrophage and smooth muscle cell apoptosis within the plaque, which may contribute to both, the formation of the necrotic core and thinning of the fibrous cap<sup>[45]</sup>. Moreover, the uptake of fluorodeoxyglucose in the left anterior descending artery (LAD), which is a potential marker of inflammatory activity of the vessel wall, has been significantly correlated with EAT volume in one study<sup>[46]</sup>. Also, in an intravascular ultrasound analysis of LADs performed by Prati *et al*<sup>[47]</sup>, most of the plaques with positive remodeling were located towards the epicardial side of the vessel rather than at the myocardial one (Figure 4). Finally, a recent study performed by Alexopoulos *et al*<sup>[48]</sup>

linked non-invasive characteristics of plaque vulnerability by MSCT with EAT, since it was observed that EAT was an independent predictor of coronary artery calcium [exp(B) = 3.916,  $P < 0.05$ ], atherosclerotic plaques of any type [exp(B) = 4.532,  $P < 0.01$ ], non-calcified plaques [exp(B) = 3.849,  $P < 0.01$ ], and obstructive CAD [exp(B) = 3.824,  $P < 0.05$ ]. Therefore, the possible mechanisms and pathways through which EAT could be related to plaque vulnerability are many, of significant importance, and a growing body of evidence supporting this association is currently being acquired.

Finally and although at this stage, many basic and cross-sectional studies have shown positive associations between increased EAT and the development and (now) the instability of the atherosclerotic process, these findings should be still interpreted as hypothesis generating and EAT measurement cannot be recommended for clinical practice. However, the scientific basis of the relationship between EAT and the aforementioned phenomena seem to be solid and warrants further studies. Since EAT can be measured by non invasive methods such as transthoracic 2D echocardiography (Figure 5), MSCT and magnetic resonance imaging<sup>[49-51]</sup>, its clinical use for primary prevention purposes could be readily available. A critical aspect in the near future will be the assessment of the incremental predictive value of EAT over established cardiovascular risk factors, if are proved or, more convincingly a cause-effect interaction is established, the introduction of EAT measurement into clinical practice



**Figure 5** Echocardiogram in the parasternal long-axis view revealing a large amount of epicardial fat (thickness of 6 mm) over the free wall of the right ventricle (blue line) of the patient in figure 1. RV: Right ventricle, LV: Left ventricle, LA: Left atrium; Ao: Aortic root.

could be taken as one step forward to the “holy grail” for the effective risk stratification<sup>[52]</sup> and prevention of coronary thrombotic events.

## REFERENCES

- 1 **Bonow RO**, Smaha LA, Smith SC, Mensah GA, Lenfant C. World Heart Day 2002: the international burden of cardiovascular disease: responding to the emerging global epidemic. *Circulation* 2002; **106**: 1602-1605 [PMID: 12270848 DOI: 10.1161/01.CIR.0000035036.22612.2B]
- 2 **Virmani R**, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1262-1275 [PMID: 10807742 DOI: 10.1161/01.ATV.20.5.1262]
- 3 **Cheruvu PK**, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, Virmani R, Muller JE. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. *J Am Coll Cardiol* 2007; **50**: 940-949 [PMID: 17765120]
- 4 **Fujii K**, Kawasaki D, Masutani M, Okumura T, Akagami T, Sakoda T, Tsujino T, Ohyanagi M, Masuyama T. OCT assessment of thin-cap fibroatheroma distribution in native coronary arteries. *JACC Cardiovasc Imaging* 2010; **3**: 168-175 [PMID: 20159644]
- 5 **Miyamoto Y**, Okura H, Kume T, Kawamoto T, Neishi Y, Hayashida A, Yamada R, Imai K, Saito K, Yoshida K. Plaque characteristics of thin-cap fibroatheroma evaluated by OCT and IVUS. *JACC Cardiovasc Imaging* 2011; **4**: 638-646 [PMID: 21679899]
- 6 **Alfonso F**, Virmani R. New morphological insights on coronary plaque rupture: bridging the gap from anatomy to clinical presentation? *JACC Cardiovasc Interv* 2011; **4**: 83-86 [PMID: 21251633]
- 7 **Stone GW**, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364**: 226-235 [PMID: 21247313 DOI: 10.1056/NEJMoa1002358]
- 8 **Alfonso F**. Noninvasive detection of vulnerable plaques: are we there yet? *J Am Coll Cardiol* 2010; **55**: 1163; author reply 1163-1164 [PMID: 20223375]
- 9 **Ito T**, Nasu K, Terashima M, Ehara M, Kinoshita Y, Ito T, Kimura M, Tanaka N, Habara M, Tsuchikane E, Suzuki T. The impact of epicardial fat volume on coronary plaque vulnerability: insight from optical coherence tomography analysis. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 408-415 [PMID: 22294682]
- 10 **Motoyama S**, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009; **54**: 49-57 [PMID: 19555840]
- 11 **Motoyama S**, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007; **50**: 319-326 [PMID: 17659199]
- 12 **Marchington JM**, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. *Comp Biochem Physiol B* 1989; **94**: 225-232 [PMID: 2591189]
- 13 **Sacks HS**, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007; **153**: 907-917 [PMID: 17540190]
- 14 **Corradi D**, Maestri R, Callegari S, Pastori P, Goldoni M, Lungu TV, Bordini C. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. *Cardiovasc Pathol* 2004; **13**: 313-316 [PMID: 15556777]
- 15 **Iacobellis G**, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2005; **2**: 536-543 [PMID: 16186852]
- 16 **Marchington JM**, Pond CM. Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro. *Int J Obes* 1990; **14**: 1013-1022 [PMID: 2086494]
- 17 **Iacobellis G**, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. *Trends Endocrinol Metab* 2011; **22**: 450-457 [PMID: 21852149]
- 18 **Iacobellis G**, Barbaro G. The double role of epicardial adipose tissue as pro- and anti-inflammatory organ. *Horm Metab Res* 2008; **40**: 442-445 [PMID: 18401833 DOI: 10.1055/s-2008-1062724]
- 19 **Iacobellis G**, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. *J Clin Endocrinol Metab* 2005; **90**: 6300-6302 [PMID: 16091479]
- 20 **Rabkin SW**. Epicardial fat: properties, function and relationship to obesity. *Obes Rev* 2007; **8**: 253-261 [PMID: 17444966]
- 21 **Yorgun H**, Canpolat U, Hazırolan T, Ateş AH, Sunman H, Dural M, Sahiner L, Kaya EB, Aytemir K, Tokgözoğlu L, Kabakçı G, Oto A. Increased epicardial fat tissue is a marker of metabolic syndrome in adult patients. *Int J Cardiol* 2011; Epub ahead of print [PMID: 21925747]
- 22 **Sicari R**, Sironi AM, Petz R, Frassi F, Chubuchny V, De Marchi D, Positano V, Lombardi M, Picano E, Gastaldelli A. Pericardial rather than epicardial fat is a cardiometabolic risk marker: an MRI vs echo study. *J Am Soc Echocardiogr* 2011; **24**: 1156-1162 [PMID: 21795020]
- 23 **Iacobellis G**, Sharma AM. Epicardial adipose tissue as new cardio-metabolic risk marker and potential therapeutic target in the metabolic syndrome. *Curr Pharm Des* 2007; **13**: 2180-2184 [PMID: 17627550]
- 24 **de Feyter PJ**. Epicardial adipose tissue: an emerging role for the development of coronary atherosclerosis. *Clin Cardiol* 2011; **34**: 143-144 [PMID: 21400540 DOI: 10.1002/clc.20893]
- 25 **Aydin H**, Toprak A, Deyneli O, Yazici D, Tarçın O, Sancak S, Yavuz D, Akalin S. Epicardial fat tissue thickness correlates with endothelial dysfunction and other cardiovascular risk factors in patients with metabolic syndrome. *Metab Syndr Relat Disord* 2010; **8**: 229-234 [PMID: 20156077 DOI: 10.1089/met.2009.0080]
- 26 **Djaberi R**, Schuijff JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. *Am J Cardiol* 2008; **102**: 1602-1607

- [PMID: 19064012]
- 27 **Rosito GA**, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, O'Donnell CJ, Fox CS. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 2008; **117**: 605-613 [PMID: 18212276]
  - 28 **Liu J**, Fox CS, Hickson DA, May WL, Ding J, Carr JJ, Taylor HA. Pericardial fat and echocardiographic measures of cardiac abnormalities: the Jackson Heart Study. *Diabetes Care* 2011; **34**: 341-346 [PMID: 21228247]
  - 29 **Xu Y**, Cheng X, Hong K, Huang C, Wan L. How to interpret epicardial adipose tissue as a cause of coronary artery disease: a meta-analysis. *Coron Artery Dis* 2012; **23**: 227-233 [PMID: 22361934 DOI: 10.1097/MCA.0b013e328351ab2c]
  - 30 **Mazurek T**, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; **108**: 2460-2466 [PMID: 14581396 DOI: 10.1161/01.CIR.0000099542.57313.C5]
  - 31 **Salgado-Somoza A**, Teijeira-Fernández E, Rubio J, Couso E, González-Juanatey JR, Eiras S. Coronary artery disease is associated with higher epicardial retinol-binding protein 4 (RBP4) and lower glucose transporter (GLUT) 4 levels in epicardial and subcutaneous adipose tissue. *Clin Endocrinol (Oxf)* 2012; **76**: 51-58 [PMID: 21645024 DOI: 10.1111/j.1365-2265.2011.04140.x]
  - 32 **Teijeira-Fernandez E**, Eiras S, Shamagian LG, Somoza AS, Delgado C, Gonzalez-Juanatey JR. Lower epicardial adipose tissue adiponectin in patients with metabolic syndrome. *Cytokine* 2011; **54**: 185-190 [PMID: 21330150]
  - 33 **Cheng KH**, Chu CS, Lee KT, Lin TH, Hsieh CC, Chiu CC, Voon WC, Sheu SH, Lai WT. Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. *Int J Obes (Lond)* 2008; **32**: 268-274 [PMID: 17878891]
  - 34 **Fain JN**, Sacks HS, Bahouth SW, Tichansky DS, Madan AK, Cheema PS. Human epicardial adipokine messenger RNAs: comparisons of their expression in substernal, subcutaneous, and omental fat. *Metabolism* 2010; **59**: 1379-1386 [PMID: 20116810]
  - 35 **Hirata Y**, Kurobe H, Akaike M, Chikugo F, Hori T, Bando Y, Nishio C, Higashida M, Nakaya Y, Kitagawa T, Sata M. Enhanced inflammation in epicardial fat in patients with coronary artery disease. *Int Heart J* 2011; **52**: 139-142 [PMID: 21646734]
  - 36 **Ishikawa Y**, Akasaka Y, Suzuki K, Fujiwara M, Ogawa T, Yamazaki K, Niino H, Tanaka M, Ogata K, Morinaga S, Ebihara Y, Kawahara Y, Sugiura H, Takimoto T, Komatsu A, Shinagawa T, Taki K, Satoh H, Yamada K, Yanagida-Iida M, Shimokawa R, Shimada K, Nishimura C, Ito K, Ishii T. Anatomic properties of myocardial bridge predisposing to myocardial infarction. *Circulation* 2009; **120**: 376-383 [PMID: 19620504]
  - 37 **Ishikawa Y**, Kawawa Y, Kohda E, Shimada K, Ishii T. Significance of the anatomical properties of a myocardial bridge in coronary heart disease. *Circ J* 2011; **75**: 1559-1566 [PMID: 21467656 DOI: 10.1253/circj/cj-10-1278]
  - 38 **Ishikawa Y**, Ishii T, Asuwa N, Masuda S. Absence of atherosclerosis evolution in the coronary arterial segment covered by myocardial tissue in cholesterol-fed rabbits. *Virchows Arch* 1997; **430**: 163-171 [PMID: 9083520 DOI: 10.1007/BF01008038]
  - 39 **Schoenhagen P**, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and direction of arterial remodeling in stable versus unstable coronary syndromes: an intravascular ultrasound study. *Circulation* 2000; **101**: 598-603 [PMID: 10673250 DOI: 10.1161/01.CIR.101.6.598.]
  - 40 **Burke AP**, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodeling in coronary atherosclerosis. *Circulation* 2002; **105**: 297-303 [PMID: 11804983 DOI: 10.1161/hc0302.102610]
  - 41 **Kolodgie FD**, Narula J, Guillo P, Virmani R. Apoptosis in human atherosclerotic plaques. *Apoptosis* 1999; **4**: 5-10 [PMID: 14634290]
  - 42 **Libby P**. Inflammation in atherosclerosis. *Nature* 2002; **420**: 868-874 [PMID: 12490960 DOI: 10.1038/nature01323]
  - 43 **Sukhova GK**, Schönbeck U, Rabkin E, Schoen FJ, Poole AR, Billingham RC, Libby P. Evidence for increased collagenolysis by interstitial collagenases-1 and -3 in vulnerable human atherosclerotic plaques. *Circulation* 1999; **99**: 2503-2509 [PMID: 10330380 DOI: 10.1161/01.CIR.99.19.2503]
  - 44 **Malek AM**, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999; **282**: 2035-2042 [PMID: 10591386 DOI: 10.1001/jama.282.16.2035]
  - 45 **Geng YJ**, Henderson LE, Levesque EB, Muszynski M, Libby P. Fas is expressed in human atherosclerotic intima and promotes apoptosis of cytokine-primed human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 1997; **17**: 2200-2208 [PMID: 9351390 DOI: 10.1161/01.ATV.17.10.2200]
  - 46 **Saam T**, Rominger A, Wolpers S, Nikolaou K, Rist C, Greif M, Cumming P, Becker A, Foerster S, Reiser MF, Bartenstein P, Hacker M. Association of inflammation of the left anterior descending coronary artery with cardiovascular risk factors, plaque burden and pericardial fat volume: a PET/CT study. *Eur J Nucl Med Mol Imaging* 2010; **37**: 1203-1212 [PMID: 20300933 DOI: 10.1007/s00259-010-1432-2]
  - 47 **Prati F**, Arbustini E, Labellarte A, Sommariva L, Pawlowski T, Manzoli A, Pagano A, Motolese M, Boccaneli A. Eccentric atherosclerotic plaques with positive remodelling have a pericardial distribution: a permissive role of epicardial fat? A three-dimensional intravascular ultrasound study of left anterior descending artery lesions. *Eur Heart J* 2003; **24**: 329-336 [PMID: 12581680]
  - 48 **Alexopoulos N**, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. *Atherosclerosis* 2010; **210**: 150-154 [PMID: 20031133]
  - 49 **Iacobellis G**, Willens HJ, Barbaro G, Sharma AM. Threshold values of high-risk echocardiographic epicardial fat thickness. *Obesity (Silver Spring)* 2008; **16**: 887-892 [PMID: 18379565 DOI: 10.1038/oby.2008.6.]
  - 50 **Iacobellis G**, Ribaudo MC, Assael F, Vecchi E, Tiberti C, Zappaterreno A, Di Mario U, Leonetti F. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. *J Clin Endocrinol Metab* 2003; **88**: 5163-5168 [PMID: 14602744]
  - 51 **Iacobellis G**, Malavazos AE, Corsi MM. Epicardial fat: from the biomolecular aspects to the clinical practice. *Int J Biochem Cell Biol* 2011; **43**: 1651-1654 [PMID: 21967993]
  - 52 **Hernando L**, Corros C, Gonzalo N, Hernández-Antolin R, Bañuelos C, Jiménez-Quevedo P, Bernardo E, Fernández-Ortiz A, Escaned J, Macaya C, Alfonso F. Morphological characteristics of culprit coronary lesions according to clinical presentation: insights from a multimodality imaging approach. *Int J Cardiovasc Imaging* 2013; **29**: 13-21 [PMID: 22527256 DOI: 10.1007/s10554-012-0043-3]

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## Sphingolipids in cardiovascular and cerebrovascular systems: Pathological implications and potential therapeutic targets

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### Abstract

The sphingolipid metabolites ceramide, sphingosine, and sphingosine-1-phosphate (S1P) and its enzyme sphingosine kinase (SphK) play an important role in the regulation of cell proliferation, survival, inflammation, and cell death. Ceramide and sphingosine usually inhibit proliferation and promote apoptosis, while its metabolite S1P phosphorylated by SphK stimulates growth and suppresses apoptosis. Because these metabolites are interconvertible, it has been proposed that it is not the absolute amounts of these metabo-

lites but rather their relative levels that determine cell fate. The relevance of this "sphingolipid rheostat" and its role in regulating cell fate has been borne out by work in many labs using many different cell types and experimental manipulations. A central finding of these studies is that SphK is a critical regulator of the sphingolipid rheostat, as it not only produces the pro-growth, anti-apoptotic messenger S1P, but also decreases levels of pro-apoptotic ceramide and sphingosine. Activation of bioactive sphingolipid S1P signaling has emerged as a critical protective pathway in response to acute ischemic injury in both cardiac and cerebrovascular disease, and these observations have considerable relevance for future potential therapeutic targets.

**Key words:** Sphingolipids; Sphingosine-1-phosphate; Sphingosine kinase; Ceramide kinase

**Core tip:** The sphingolipid pathway has received considerable attention recently, because its active metabolites appear to have salutary effects on cytoprotection in experimental cardiac and cerebral ischemia. Both inhibitors and antagonists of the sphingolipid sphingosine-1-phosphate (S1P) pathway appear to limit ischemic injury through a variety of mechanisms. Because of the clinical availability of Fingolimod (FTY720), a S1P analog, for use in multiple sclerosis, preclinical and clinical studies should focus on the development of this and similar pharmaceuticals for a new indication.

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## INTRODUCTION

Sphingolipids were first described in late 19<sup>th</sup> century and have long been viewed as merely ubiquitous components of the cell membrane. Recently, sphingolipids have been increasingly reevaluated because they are now recognized to not only regulate vital cell functions, but also form cell membrane microdomain “lipid rafts” for integrating cell signaling<sup>[1,2]</sup>. Sphingolipids are formed *via* the metabolism of sphingomyelin, a ubiquitous constituent of the plasma membrane, or by *de novo* synthesis. Enzymatic pathways result in the formation of several different lipid mediators such as ceramide, sphingosine, and sphingosine-1-phosphate (S1P). Several studies now showed that these sphingolipid mediators and their enzymes, especially sphingosine kinase (SphK), are likely to have an integral role in different cell processes including proliferation, inflammation, apoptosis and migration. The mode of action of each sphingolipid is different. A significant body of research now indicates that sphingolipids are intimately involved in disease progression and that these lipids, together with associated enzymes and receptors, can provide effective drug targets for the treatment of pathological states. This review will highlight the current knowledge of research where sphingolipids are involved with focus on cardiovascular and cerebrovascular disease, and the mechanisms of action of each sphingolipid mediator. In addition, the therapeutic potential of drugs that alter sphingolipid actions with focus on SphK/S1P signaling pathway that appears to be a target of interest for therapeutic manipulation.

## METABOLISM AND SIGNALING PATHWAYS OF SPHINGOLIPIDS

Sphingolipids are complex lipids comprised of a sphingoid base, and are one of the major lipid components of cell membrane as well as glycerophospholipid and cholesterol. A schematic diagram of sphingolipid metabolism is depicted in Figure 1. *De novo* biosynthesis of sphingolipids begins with the conversion of serine and palmitoyl-CoA into 3-ketosphinganine. 3-ketosphinganine is then converted to dihydrosphingosine. Dihydroceramide synthase acrylates dihydrosphingosine to form dihydroceramide, which is then reduced to ceramide by dihydroceramide desaturase. Sphingomyelin can also be converted to ceramide by sphingomyelin synthase, and a reverse reaction is catalyzed by sphingomyelinase. Ceramide can also be degraded by ceramidase to form sphingosine, which can, in turn, be phosphorylated to S1P by two enzymes SphK1 or 2. The bioactive lipid ceramide-1-phosphate (C1P) is formed by phosphorylation of ceramide by ceramide kinase; it can also be reverted to ceramide by ceramide phosphatase. The reverse reaction from S1P is catalyzed by sphingosine-1-phosphate phosphatases and ceramide synthase that yield sphingosine and ceramide respectively<sup>[3]</sup>. S1P can be further metabolized by S1P lyase, yielding hexadecenal and ethanolamine phosphate<sup>[4]</sup>.

### Ceramide

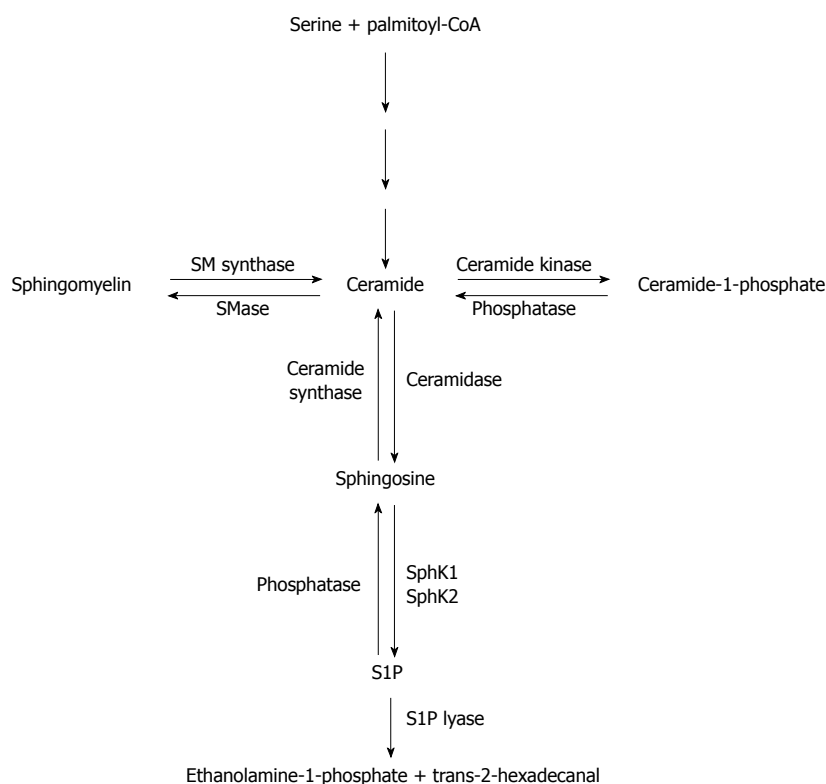
Ceramides are a family of lipids that consist of sphingosine covalently linked to a fatty acid and are densely located at the cell membrane. Ceramides are the key component lipids that constitute sphingomyelin, the major source of the human sphingolipids, and one of the major components which form the phospholipid bilayer<sup>[5]</sup>. Discovery over the last few decades reveal that all stress stimuli, such as inflammatory mediators, heat, ultraviolet radiation, hypoxia, chemotherapeutics, and oxidative stress increase ceramide production as part of an evolutionarily conserved cellular response<sup>[6-13]</sup> and toll like receptor 4 seems to be involved in ceramide synthesis<sup>[14]</sup>. Consecutively ceramides not only promote cell cycle arrest and promote apoptosis, a form of programmed cell death, but also play an important role in the regulation of autophagy, cell differentiation, and inflammatory responses<sup>[9,15-18]</sup>. Ceramide is also involved in dephosphorylation and inactivation of one major mediator of cell survival; protein kinase Akt, (Akt/PKB)<sup>[19-21]</sup>. On the other hand, recent data shows that phosphorylated ceramide, C1P seems to have the opposite effects from ceramide; by inducing prosurvival functions, such as cell growth and survival, control of inflammation and mediation of macrophage migration<sup>[22-24]</sup>.

### Sphingosine

Sphingosine is also a bioactive sphingolipid formed from ceramide as a result of ceramidase activity. It was first described as the physiological inhibitor of the survival signal protein kinase C (PKC), and was also found to up-regulate caspase 3 in the cascade of apoptosis<sup>[25-28]</sup>. There are many reports showing that PKC is inhibited by exogenous sphingosine, and it has been demonstrated that endogenously generated sphingosine is a potent PKC inhibitor<sup>[29]</sup>. In turn, sphingosine can control the activity of other key enzymes involved in the regulation of metabolic or cell signaling pathways such as the Mg<sup>2+</sup> dependent form of phosphatidate phosphohydrolase<sup>[30,31]</sup>, phospholipase D (PLD)<sup>[32]</sup>, or diacylglycerol kinase<sup>[33,34]</sup>. Although there is abundant evidence that sphingosine is toxic to cells<sup>[25,28]</sup>, diverse function by concentration dependence of sphingosine has been reported. Vessey *et al.*<sup>[35]</sup> recently reported that at lower dose (submicromolar), a more physiologic concentrations, sphingosine has been shown to be cardioprotective in isolated Langendorff-perfused rat hearts subjected to ischemia/reperfusion injury. Unlike S1P, sphingosine-induced cardioprotection seems to be mediated by cyclic nucleotide-dependent protein kinase A and G (PKA and PKG) pathways<sup>[35]</sup>. While, at the higher concentrations usually employed, sphingosine is toxic to cells<sup>[27]</sup>.

### S1P

S1P is a bioactive lipid signaling molecule formed when either one of two isoforms of the enzyme SphK1 or 2 catalyzes the addition of a phosphate group to sphingosine. S1P exerts a wide variety of biological activities in



**Figure 1 Schematic outline of sphingolipid metabolism.** Names of the major intermediates and abbreviations of the enzymes involved are included. SM: Sphingomyelin; SphK: Sphingosine kinase; S1P: Sphingosine-1-phosphate.

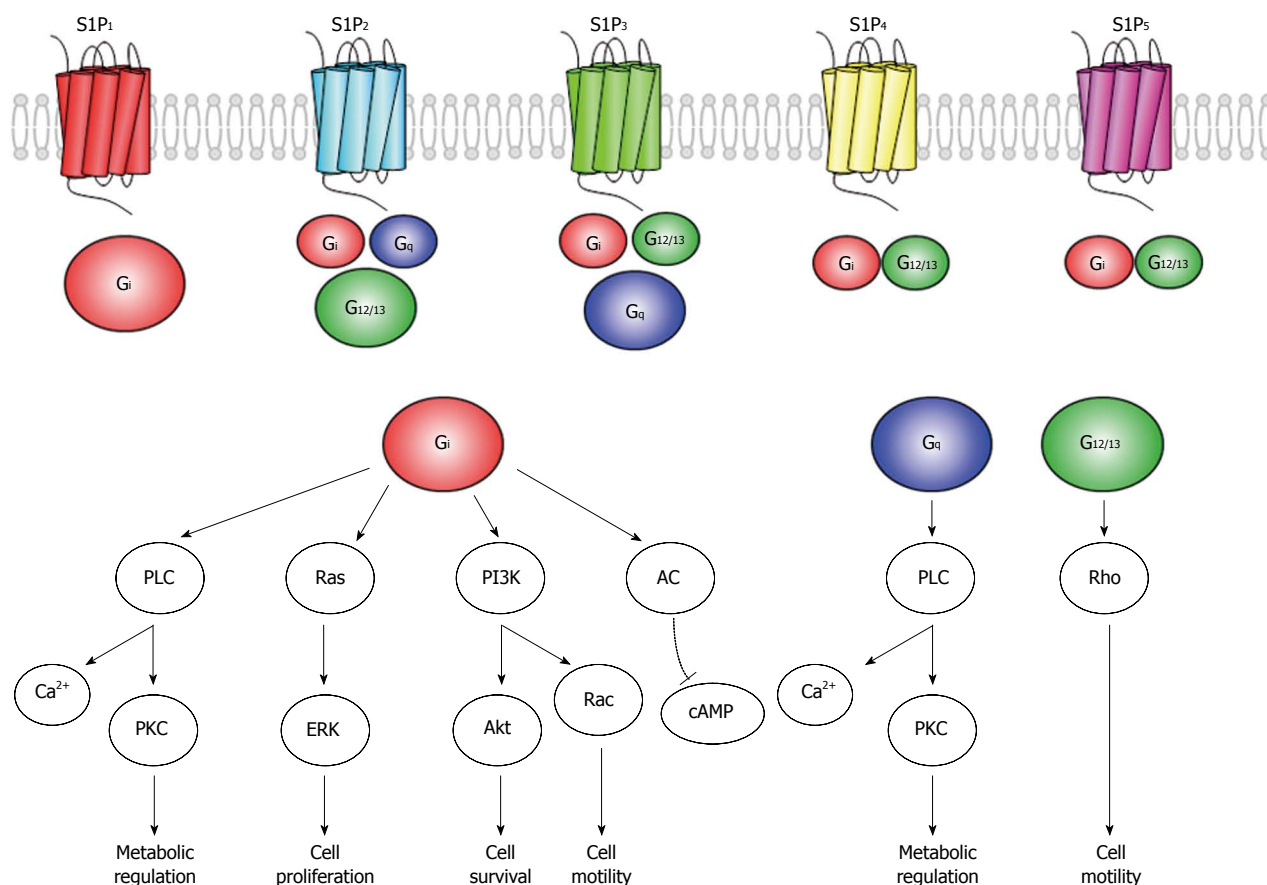
many eukaryotic cell types<sup>[36-38]</sup>. It was initially proposed to act as an intracellular second messenger, based on the ability of extracellular growth factors to activate SphK and increase intracellular S1P levels. The discovery and cloning of five G protein-coupled receptors (S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, S1P<sub>4</sub>, S1P<sub>5</sub>) expressed on the cell membrane has stimulated the notion that S1P is an extracellular signaling ligand, regulating a host of cellular functions such as proliferation, survival, immunomodulation, apoptosis, migration, cytoskeletal organization, and differentiation/morphogenesis<sup>[39]</sup>. Basal plasma and serum concentration levels of S1P are generally low ranging within 200-900 nmol/L, but can increase rapidly and transiently when cells are exposed to various agonists<sup>[40,41]</sup>. The concentration of S1P is controlled by two enzyme, SphK and S1P lyase. While SphK activity can be upregulated by a variety of growth factors, S1P lyase activity in other hand is constantly at the high level, and this makes the intracellular S1P level very low in most tissues. However, erythrocytes and platelets have low S1P lyase activity resulting in high S1P concentration in blood plasma<sup>[38,42]</sup>. This concentration gradient is presumed to provide the basis for the integral role for the bioactivity of S1P involved in lymphocyte trafficking<sup>[43]</sup>.

After the discovery of S1P receptors, there has been extensive work aimed at understanding the role of S1P as extracellular ligands. A schematic of the S1P receptors are shown in Figure 2. S1P mediates its effects through binding to G protein-coupled receptors (S1P<sub>1-5</sub>) which

activates a variety of signaling *via* transduction of G proteins isoforms (G<sub>s</sub>, G<sub>i</sub>, G<sub>q</sub>, and G<sub>12/13</sub>). The prosurvival phosphatidylinositol-3-kinase (PI3K)/Akt have been shown to be downstream molecules regulated by the S1P<sub>1</sub> receptor signaling, Akt activation is a principal factor in the prevention of apoptosis<sup>[44,45]</sup>. S1P also stimulates cell growth and proliferation *via* activation of mitogen-activated protein kinase extracellular signal-regulated kinases (ERK)<sup>[46]</sup>. It is believed that elevated ERK phosphorylation plays a role in cell survival and proliferation in the penumbra, and ERK activity may block apoptosis by enhancing the level of the antiapoptotic protein Bcl-2 through cAMP responsive element binding protein activation<sup>[44]</sup>. S1P is also assumed to prevent necrosis mediated by the PKC $\epsilon$  pathway<sup>[47]</sup>.

### Sphingosine kinase

The synthesis of S1P is catalyzed by SphK which is responsible for linking a phosphate group to sphingosine. There are two isozymes of SphK designated as SphK1 and SphK2. SphK1 and SphK2 show different subcellular localizations and enzymatic properties as well as different expression in various tissues. Mouse and human SphK1 exhibit substantial homology and SphK2 is highly homologous to SphK1 except for 240 additional amino acids located at the N terminus and in the center of the enzyme. The genes encoding these isozymes are localized on different chromosomes<sup>[48]</sup>. Genetic deletion of both isozymes results in fetal death from severe bleeding,



**Figure 2** Schematic outline of sphingosine-1-phosphate signaling through receptors. S1P: Sphingosine-1-phosphate; ERK: Extracellular signal-regulated kinases; PKC: Protein kinase C; PLC: Phospholipase C.

inadequate vasculogenesis, and incomplete neural tube closure<sup>[48,49]</sup>. In contrast, mice null for either the SphK1 or the SphK2 isozyme exhibit normal development and are otherwise unremarkable in the basal state<sup>[49]</sup>. It is presumed that these isozymes have the complementary functions. The regulation of SphK activity is complex. It is stimulated by G-protein coupled receptor agonists (muscarinic receptor agonists<sup>[50]</sup>, formyl peptide<sup>[51]</sup>, nucleotides, bradykinin<sup>[52]</sup>, lysophosphatidic acid<sup>[53]</sup>, and S1P<sup>[54]</sup>), agonists at receptor tyrosine kinases (platelet-derived growth factor<sup>[55]</sup>, endothelial growth factor<sup>[56]</sup>, nerve growth factor<sup>[57]</sup>, fibroblast growth factor<sup>[57]</sup>, vascular endothelial growth factor<sup>[58]</sup>), immunoglobulin receptor crosslinking<sup>[59]</sup>, monoganglioside (GM1)<sup>[60]</sup>, estrogen<sup>[61]</sup> and activators of PKC $\epsilon$ <sup>[62]</sup>. Both TNF- $\alpha$  and phorbol ester, which stimulates PKC, phosphorylate and thus activate SphK1 at serine225 mediated by ERK1/2<sup>[63,64]</sup>. The tumor necrosis factor (TNF)  $\alpha$  response requires binding by TNF receptor-associated factor-2 (TRAF2). Other interacting proteins that stimulate SphK include delta-catenin/NPRAP (neural plakophilin-related armadillo repeat protein), aminoacylase 1, and eukaryotic elongation factor 1A (EEF1A)<sup>[65]</sup>. Reported inhibitory interacting proteins are SKIP (SK1-interacting protein), PECAM-1 (platelet endothelial adhesion molecule-1), and FHL-2 suppressed VEGF-induced PI-3 kinase/Akt activation *via*

interactions with SphK1<sup>[66-69]</sup>.

Despite the structural similarities and even though it catalyses the production of S1P, SphK2 has shown to have opposing actions to SphK1<sup>[70]</sup>. Thus, SphK2 inhibits cell growth and enhances apoptosis, in part by regulating ceramide levels<sup>[70]</sup>. Downregulation of SphK2 reduced conversion of sphingosine to ceramide, while downregulation of SphK1 increased it. The pathway of sphingosine into pro-apoptotic ceramide is dependent on SphK2, but not SphK1, acting in concert with S1P phosphohydrolase 1<sup>[71]</sup>. And also interestingly, there are organ specific deviations of SphK. While SphK1 is the more abundant isozyme in lung, spleen, kidney, heart, renal proximal tubules and cardiomyocytes, SphK2 isozyme predominates in the brain<sup>[72-74]</sup>. The intracellular locations of two enzymes are also different. SphK1 is localized predominantly in the cytoplasm while, SphK2 is mainly localized in the nucleus<sup>[75]</sup>. The reason of this deviation difference is that SphK1 has two functional nuclear export signal (NES) sequences which positively direct SphK1 to an extranuclear location. On the other hand, a nuclear localization signal (NLS) sequence has been found in SphK2 which keeps SphK2 in the nucleus and NES shuttles SphK2 between the cytoplasm and the nucleus according to demand<sup>[75]</sup>. The underlying reasons for this and its functions have yet to be elucidated.

## ROLE OF SPHINGOLIPIDS IN CARDIOVASCULAR DISEASE

### S1P in cardioprotection

The cardioprotective effect of S1P was first reported in 2001<sup>[76]</sup>. In neonatal rat cardiac myocytes, exogenously applied S1P enhanced cardiac myocyte survival during hypoxia<sup>[76]</sup>. Subsequent studies were undertaken using cultured adult mouse cardiac myocytes subjected to hypoxia *in vitro* that mimics ischemia *in vivo* during coronary artery occlusion. This system permitted measurements of S1P effects on myocyte viability during stress and activation of cell signaling from plasma membrane to mitochondria. There were three major findings that advanced understanding of S1P prosurvival effects during hypoxia<sup>[77]</sup>. First, it was found that S1P<sub>1</sub> receptors are abundantly expressed by adult mouse cardiac myocytes<sup>[78]</sup>. Second, exogenously applied S1P enhanced survival during prolonged *in vitro* hypoxia through mechanisms that required S1P<sub>1</sub> receptor function and G protein Gi-independent activation of the prosurvival kinase Akt/PKB. Finally, Akt-mediated phosphorylation of myocyte substrates that interact with mitochondria, such as GSK-3 and BAD, contributed to cardioprotection. In these studies the selective S1P<sub>1</sub> receptor agonist SEW2871 and the S1P analog FTY720 were as effective as S1P in preserving myocytes viability during hypoxia<sup>[77]</sup>. In contrast, Means *et al.*<sup>[79]</sup> were unable to demonstrate prosurvival signaling mediated by the S1P<sub>1</sub> receptor. The divergent observations surrounding the cardioprotective effects of S1P<sub>1</sub> agonism may result from methodologic differences. Even though, these data strongly suggest that the S1P<sub>1</sub> receptor, which is the most abundant S1P receptor subtype in cardiac myocytes, is at least partially responsible for S1P-mediated prosurvival signaling and for maintaining myocytes viability during hypoxia<sup>[77]</sup>, and during hypoxia/reoxygenation<sup>[37]</sup>. In a study of the other receptors, it was shown that combined deletion of S1P<sub>2</sub> and S1P<sub>3</sub> receptors augmented infarct size in mice subjected to ischemia/reperfusion injury<sup>[80]</sup>. In these hearts, activation of Akt was markedly attenuated compared to wildtype mice, but the absence of either receptor subtype alone affected neither infarct size nor Akt activation after ischemia/reperfusion injury. S1P augmented Akt activity in control murine myocytes, but was not effective in the double knockout cells<sup>[80]</sup>. Thus, these observations suggest that the less abundant cardiac myocyte S1P receptors (S1P<sub>2</sub> and S1P<sub>3</sub>) may also be necessary for cell survival during ischemia/reperfusion injury.

In SphK1 null ventricular myocytes subjected to *in vitro* hypoxia, cell death and cytochrome c release were greater than in wild-type controls<sup>[36]</sup>. Exogenous S1P enhanced survival of both wild-type and SphK1 null cells. GM-1 treatment, which activates PKC domain and subsequently upregulates SphK to produce S1P, induced cytoprotection in wild-type cardiac myocytes but not in SphK1 null cells. These observations indicate that GM-1 activates SphK1, presumably *via* PKC $\epsilon$ -mediated phos-

phorylation. Interestingly, the beneficial effects of GM-1 on wild-type cardiac myocytes were abolished by pretreatment with either an S1P<sub>1</sub> receptor antagonist or pertussis toxin, which ADP-ribosylates and thereby inactivates G<sub>i</sub>, suggesting that endogenous S1P was transported to the extracellular space for activation of its cognate G-protein coupled receptors<sup>[36]</sup>. A potential mechanism for extrusion of S1P is *via* ABC transporters, which have been demonstrated in a variety of cell types<sup>[81,82]</sup>, as well as in murine and human hearts<sup>[83,84]</sup>. Recently, a specific S1P transporter, SPN2, which also transports the phosphorylated form of FTY720, has also been described<sup>[85]</sup>. Knapp *et al.*<sup>[86]</sup> also mentioned the importance of the S1P/ceramide levels ratio which could be responsible for increased apoptosis in the myocardial infarction in the rat.

### Sphingosine kinase in cardioprotection

As noted above, GM-1 enhanced the survival of cardiac fibroblasts subjected either to PKC inhibition or to C2-ceramide (N-acetyl-sphingoid bases) treatment<sup>[62]</sup>. GM-1 also increased S1P levels, an effect abrogated by the SphK inhibitor, DMS<sup>[62]</sup>. Using isolated adult mouse hearts, exogenous S1P and GM-1 separately induced substantial resistance to ischemia-reperfusion injury in wild-type mice<sup>[87]</sup>. Similar experiments were reported by Lecour *et al.*<sup>[88]</sup> in isolated rat heart. The importance of the prosurvival kinase, PKC $\epsilon$ , was emphasized by experiments in which GM-1 proved to be ineffective in PKC $\epsilon$ -null hearts. In addition, GM-1, but not exogenous S1P, stimulated translocation of activated PKC $\epsilon$  to myocyte particulate fractions<sup>[87]</sup>. Nevertheless, exogenously administered S1P was effective both in isolated PKC $\epsilon$ -null hearts subjected to ischemia/reperfusion injury<sup>[87]</sup> and in isolated cardiac myocytes from these hearts subjected to hypoxia<sup>[36]</sup>. Thus, S1P acting at cell surface receptors or activation of intracellular SphK confers cardioprotection during acute ischemia/reperfusion injury. Consistent with this hypothesis, it was shown that PKC $\epsilon$  activation is essential for cardioprotection induced by ischemic preconditioning (IPC)<sup>[89]</sup>. PKC $\epsilon$  peptide agonists mimicked preconditioning effects on contractile recovery and tissue viability in wild-type hearts after prolonged ischemia-reperfusion injury<sup>[90]</sup>. In contrast, inducible cardioprotection was blocked by PKC peptide antagonists and targeted deletion of the PKC $\epsilon$  gene<sup>[91]</sup>. A subsequent series of experiments directly tested the hypothesis that SphK activation mediates IPC in isolated mouse hearts<sup>[90]</sup>. It was determined that IPC sufficient to reduce infarction size in wild-type hearts increased SphK localization and activity in tissue membrane fractions. Interestingly, IPC triggered SphK translocation to tissue membrane fractions in PKC $\epsilon$ -null hearts but did not enhance enzymatic activity or decrease infarction size after ischemia-reperfusion injury<sup>[90]</sup>. As noted above, DMS, the endogenous sphingolipid generated by N-methylation of sphingosine, inhibited tissue SphK activity, while 10  $\mu$ mol/L of DMS pretreatment abolished IPC-induced cardioprotection in wild-type hearts<sup>[90]</sup>. Sub-

sequent experiments elucidated unpredicted effects of low DMS concentrations on SphK<sup>[92]</sup>. In contrast to moderate dose DMS (10  $\mu$ mol/L), low-dose DMS stimulated translocation of activated PKC $\epsilon$  to tissue particulate fractions and reduced cardiac ischemia-reperfusion injury. Importantly, low-dose DMS effects were abolished in PKC $\epsilon$ -null hearts, and SphK1 was found to co-immunoprecipitate with activated PKC phosphorylated at serine729. Low-dose DMS induced translocation of total Akt from Triton-insoluble fractions to cytosol and increased activated Akt phosphorylated at serine473<sup>[92]</sup>.

When tested with the classic SphK inhibitor, DMS, the activity of SphK2 was unaffected by concentrations as high as 20  $\mu$ mol/L. Consistent with this observation, DMS was only a partial inhibitor of total cytosolic SphK activity<sup>[93]</sup>. Also SphK2 was not inhibited by the sphingosine analogue, FTY720. As noted earlier, SphK1 was efficiently inhibited by both DMS and FTY720. Furthermore, when the cytosolic fraction from SphK1 knockout mouse hearts was tested, residual activity due to SphK2 was not inhibited by DMS or FTY720<sup>[93]</sup>. These observations confirmed the specificity of SphK1 inhibition and indicated the lack of inhibition of SphK2 was not an artifact of purification. SphK2 from rat liver and spleen was also not inhibited by DMS. In contrast, l-sphingosine was an effective inhibitor of both forms<sup>[93]</sup>. Taken together, along with data obtained in SphK1-null hearts, these observations indicated that DMS inhibits only the SK1 form in the heart. Thus, prior experiments in other cells and tissues in which DMS was used as inhibitor of SphK may require reinterpretation.

The time course of SphK activity in adult rat hearts subjected to ischemia/reperfusion injury and preconditioning has been reported<sup>[94]</sup>. Cytosolic SphK activity declined by 61% during ischemia and did not recover upon reperfusion, paralleling the effects on left ventricular developed pressure (LVDP). IPC reduced the decrease in enzyme activity during ischemia by half and, upon reperfusion activity, returned to normal. LVDP recovered to 79% of control values, and infarct size was reduced. The low baseline-specific activity of SphK declined by 67% after 45 min of ischemia and remained at that level during reperfusion. IPC restored SphK activity almost to normal during reperfusion. Parallel effects were observed in mitochondria from the same hearts<sup>[94]</sup>. In these experiments<sup>[94]</sup>, total S1P in cardiac tissue was quantified by liquid chromatography followed by tandem mass spectrometry<sup>[38]</sup>. In non-preconditioned hearts, S1P content declined from base line after both ischemia and reperfusion. Preconditioned hearts had higher S1P levels after ischemia/reperfusion relative to control hearts. Treatment of non-preconditioned hearts at reperfusion (pharmacologic postconditioning) with 100 nmol/L of S1P improved recovery of LVDP. Thus, maintenance of SphK activity resulting from higher S1P levels is critical for recovery from ischemia/reperfusion injury. In this connection, the activity of S1P phosphatases and lyase has not been reported during experiments involving isch-

emia/reperfusion injury in the heart.

Despite compelling evidence that DMS modulates resistance to injury by inhibiting SphK1, however, this drug also has been shown to alter other kinases such as PKC activity<sup>[92]</sup>. Accordingly, SphK1 knockout mice have been employed in a series of subsequent studies<sup>[95,96]</sup>. SphK2 expression increased in hearts after *SphK1* gene disruption, resulting in total SphK activity half that of wild type. Although SphK1-null hearts exhibited normal hemodynamic performance under baseline conditions, contractile abnormalities and infarction were more severe after ischemia/reperfusion than in wild-type hearts<sup>[95]</sup>. As predicted, targeted disruption of the *SphK1* gene abolished IPC-induced cardioprotection<sup>[95]</sup>. Importantly, when the index ischemia time was reduced from 50 to 40 min, infarct size in the *SK1* knockout hearts declined to the level seen in the wild type hearts subjected to ischemia/reperfusion injury. At this reduced level of injury, IPC was still ineffective in producing cardioprotection in the knockout hearts. However, exogenous S1P retained the ability to induce cardioprotection in these *SphK1*-null hearts. Despite an increase in SphK2 expression in the *SphK1*-null hearts, infusion of DMS did not affect infarct size, confirming prior *in vitro* experiments and suggesting that the absence of SphK1 rather than the increased presence of SphK2 was critical to the loss of cardioprotection in myocardium null for SphK1<sup>[95]</sup>. However, Vessey *et al.*<sup>[97]</sup> recently demonstrated that myocardial damage is enhanced after ischemia/reperfusion in mice null for SphK2 and that the cardioprotective intervention of preconditioning is abolished by deletion in the *SphK2* gene. These observations are contrary to prior suggestions derived from *in vitro* models that SphK1 and SphK2 drive opposing functions that regulate cell fate<sup>[97]</sup>.

In another recent study, it was reported that previous adenoviral gene transfer of *SphK1* protected against hemodynamic deterioration and reduced creatine kinase release and arrhythmias during acute ischemia/reperfusion injury in isolated rat hearts<sup>[96]</sup>. When gene transfer was performed at the time of acute left anterior descending coronary artery ligation, studies 2 wk later revealed improved left ventricular function in the treated mice, reduced infarct size, more neovascularization, and reduced collagen content<sup>[96]</sup>.

Like IPC, ischemic postconditioning is cardioprotective<sup>[98]</sup>, and this observation has recently been extended to patients undergoing percutaneous coronary interventions<sup>[99]</sup>. To ascertain whether the SphK/S1P pathway is a determinant of successful postconditioning, isolated wild type and *SphK1*-null mouse hearts were subjected to ischemia/reperfusion injury<sup>[100]</sup>. At the onset of reperfusion, hearts selected for treatment underwent 3 brief cycles of postconditioning (5 s of ischemia followed by 5 s of reperfusion). Results were similar to the preconditioning studies cited above: hemodynamics were improved and infarction size reduced compared with untreated hearts<sup>[100]</sup>. Phospho-Akt and phospho-ERK were enhanced. None of these findings were present in *SphK1*-

null hearts. Thus, SphK1 is also critical for successful ischemic postconditioning. In this connection, it has recently been found that a ramped ischemic postconditioning protocol combined with low-dose sphingosine + S1P given at the time of reperfusion can rescue isolated hearts from as much as 90 min of ischemia<sup>[101]</sup>.

## ROLE OF SPHINGOLIPIDS IN Cerebrovascular Disease

### *Distribution and function of S1P and SphK in the brain*

While S1P signaling has long been known to mediate protection in peripheral and cardiac ischemia, only recently has this bioactive lipid pathway drawn attention in cerebral ischemia.

S1P has shown many neuroprotective mechanisms in both *in vitro* and *in vivo*. S1P is presumed to protect central nervous system through many different ways<sup>[102,103]</sup>. In addition to the above mentioned prosurvival effect of S1P, S1P may also protect the brain vasculature by reducing leukocyte adhesion secondary to altering endothelial adhesion molecule expression and preventing endothelial apoptosis through Bcl-2 activation. There is also evidence that S1P may act as a proximal trigger of cerebroprotection (both neuronal and vascular) through activation of signaling molecules such as endothelial nitric oxide synthase<sup>[102]</sup>.

In models of stroke, Kimura *et al.*<sup>[104]</sup> found that S1P concentrations in the brain were significantly decreased 3 d after ischemia. However, S1P in the brain was increased thereafter and reached a maximum 14 d after the insult. Upregulation of S1P was observed at the infarct border zone and at the infarct core, and mostly colocalized to microglia and some astrocytes, indicating that microglia may be the main source of S1P production in ischemic brain<sup>[104]</sup>.

Moreover, the S1P regulating enzymes SphKs show differential tissue expression patterns and different subcellular localization<sup>[72]</sup>. Although SphK1 has greater expression and activity than SphK2 in many organs such as lung and spleen, SphK2 expression levels are greater than SphK1 in the brain, suggesting a more prominent physiological role for SphK2 in the brain and brain vasculature<sup>[73,74]</sup>. Among brain resident cells, primary glial cells express more SphK2 mRNA than primary neurons, and the highest mRNA concentrations were found in cortex, while mRNA was least abundant in striatum<sup>[74]</sup>. Increased SphK2 was observed in response to cerebral ischemia both *in vitro* and *in vivo*<sup>[74]</sup>. As mentioned earlier, SphK2 could promote apoptosis, instead of cell survival as SphK1 shows at the non-central nervous system<sup>[70]</sup>, there is also accumulated evidence that SphK2 could play an important role as a prosurvival factor in the central nervous system<sup>[73,105,106]</sup>.

A widely used anesthetic agent isoflurane is now considered to be one of the promising therapeutic strategies for many neurological diseases including ischemic stroke<sup>[107]</sup>. Zhou *et al.*<sup>[107]</sup> reported that isoflurane given post injury attenuated brain damage after subarachnoid hemorrhage, and that the neuroprotective effect was

associated with decreased neuronal apoptosis partly through the antiapoptotic effect of sphingosine-related pathway activation including SphK1 and S1P<sub>1,3</sub> receptors. Isoflurane-mediated neuroprotection has also been examined during neonatal hypoxia ischemia through the S1P/PI3K/Akt signaling. The PI3K/Akt signaling cascade has been shown to play a key role in preventing apoptosis under hypoxic or ischemic conditions. Hypoxic preconditioning (HPC) has also been investigated in the contest of cerebral ischemia<sup>[105,108]</sup>. With respect to elucidating the molecular basis of preconditioning-induced tolerance, Yung *et al.*<sup>[106]</sup> showed that hypoxic preconditioning significantly reduced infarct volume and improved neurological outcome in wild-type and SphK1<sup>-/-</sup>, but not in SphK2<sup>-/-</sup> mice. Wacker *et al.*<sup>[105,108]</sup> also documented HPC-induced ischemic tolerance and the concomitant protection of the blood-brain-barrier depended on SphK2 signaling. SphK2-generated S1P participates in both the normal maintenance of occlusion at cytoskeletally linked cell junctions, as well as the mediation of HPC-induced increases in the expression of claudin-5 and VE-cadherin at these junctions, which may be compulsory for induction of the vasculoprotective phenotype by HPC. The present data demonstrates that SK2 is a universal mediator of isoflurane- and hypoxia-induced preconditioning.

### *Role of FTY720 in cerebrovascular disease*

FTY720 (Fingolimod) is a novel immunomodulatory agent, which in its phosphorylated form acts as a high affinity agonist of S1P receptors<sup>[109,110]</sup>. It became the first oral drug to be FDA-approved for clinical use in the treatment of multiple sclerosis. FTY720 readily crosses the blood-brain barrier and exerts a number of direct effects in the central nervous system. FTY720 is phosphorylated by SphK, mainly by SphK2<sup>[73,111]</sup>, into the active compound phospho-FTY720, which then acts on 4 of the 5 known S1P receptor subtypes (S1P<sub>1</sub>, S1P<sub>3</sub>, S1P<sub>4</sub>, S1P<sub>5</sub>), and shows neuroprotective effect against many central nervous system disease including cerebral ischemia<sup>[73,112-115]</sup>. Mechanisms include regulation of myelination and microglial activation following injury, proliferation and migration of neural precursor cells toward injury sites, and potentiation of growth-factor regulated neuronal differentiation, survival, and process extension, and also antiapoptotic and anti-inflammatory pathways<sup>[104,113,115-119]</sup>. FTY720 also exerts immunomodulatory actions by affecting lymphocyte production, trafficking, and apoptosis through S1P receptors which induces a depletion of circulating lymphocytes by preventing the egress of lymphocytes from the lymph nodes. Mechanistically, this is due to a downregulation of the S1P type 1 receptor (S1P<sub>1</sub>). Expression levels of endothelial adhesion molecules such as E-selectin, P-selectin, intracellular adhesion molecule-1 or vascular cell adhesion molecule-1 were shown to be induced by FTY720 treatment, and therefore might contribute to the prevention of early infiltration of neurotrophils and activation of microglia/macrophages. These findings suggest that anti-inflamma-

tory mechanisms, and possibly vasculoprotection, rather than direct effects on neurons, underlie the beneficial effects of fingolimod after stroke. Most of the past reports have shown beneficial effect of S1P in the field of ischemia, but by contrast, Liesz *et al.*<sup>[120]</sup> showed opposite results. These authors found that S1P treatment did show a reduction of lymphocyte brain invasion but could not achieve a significant reduction of infarct volumes and behavior dysfunction<sup>[120]</sup>. Liu *et al.*<sup>[121]</sup> recently published a systematic meta-analysis of the efficacy of FTY720 in animal model of stroke. In this study, they concluded that FTY720 reduced infarct volume and improve functional outcome. However, the authors also indicated that more experimental studies should be performed to evaluate the safety of FTY720 in the future. Thus, taken this recent scientific highlights together, it is obvious that S1P receptor pathways and sphingolipids regulating enzymes are a highly promising target in stroke treatment.

## CONCLUSION

During the past few years, a plethora of new information identifying the importance of sphingolipid signaling pathways in the cardiovascular and cerebrovascular diseases has accumulated. The potential for the development of new therapeutic agents based on this understanding is high, but this is clearly a new area of investigation that is still in its infancy.

## REFERENCES

- 1 Hanzal-Bayer MF, Hancock JF. Lipid rafts and membrane traffic. *FEBS Lett* 2007; **581**: 2098-2104 [PMID: 17382322 DOI: 10.1016/j.febslet.2007.03.019]
- 2 Nagatsuka Y, Hara-Yokoyama M, Kasama T, Takekoshi M, Maeda F, Ihara S, Fujiwara S, Ohshima E, Ishii K, Kobayashi T, Shimizu K, Hirabayashi Y. Carbohydrate-dependent signaling from the phosphatidylglucoside-based microdomain induces granulocytic differentiation of HL60 cells. *Proc Natl Acad Sci USA* 2003; **100**: 7454-7459 [PMID: 12802014 DOI: 10.1073/pnas.1232503100]
- 3 Kolesnick RN, Hemer MR. Characterization of a ceramide kinase activity from human leukemia (HL-60) cells. Separation from diacylglycerol kinase activity. *J Biol Chem* 1990; **265**: 18803-18808 [PMID: 2172234]
- 4 Serra M, Saba JD. Sphingosine 1-phosphate lyase, a key regulator of sphingosine 1-phosphate signaling and function. *Adv Enzyme Regul* 2010; **50**: 349-362 [PMID: 19914275 DOI: 10.1016/j.advenzreg.2009.10.024]
- 5 Bikman BT, Summers SA. Ceramides as modulators of cellular and whole-body metabolism. *J Clin Invest* 2011; **121**: 4222-4230 [PMID: 22045572 DOI: 10.1172/JCI57144]
- 6 Dressler KA, Mathias S, Kolesnick RN. Tumor necrosis factor- $\alpha$  activates the sphingomyelin signal transduction pathway in a cell-free system. *Science* 1992; **255**: 1715-1718 [PMID: 1313189]
- 7 Haimovitz-Friedman A, Kan CC, Ehleiter D, Persaud RS, McLoughlin M, Fuks Z, Kolesnick RN. Ionizing radiation acts on cellular membranes to generate ceramide and initiate apoptosis. *J Exp Med* 1994; **180**: 525-535 [PMID: 8046331]
- 8 Kolesnick RN, Haimovitz-Friedman A, Fuks Z. The sphingomyelin signal transduction pathway mediates apoptosis for tumor necrosis factor, Fas, and ionizing radiation. *Biochem Cell Biol* 1994; **72**: 471-474 [PMID: 7544586]
- 9 Okazaki T, Bielawska A, Bell RM, Hannun YA. Role of ceramide as a lipid mediator of 1  $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>-induced HL-60 cell differentiation. *J Biol Chem* 1990; **265**: 15823-15831 [PMID: 2394750]
- 10 Kim MY, Linardic C, Obeid L, Hannun Y. Identification of sphingomyelin turnover as an effector mechanism for the action of tumor necrosis factor  $\alpha$  and gamma-interferon. Specific role in cell differentiation. *J Biol Chem* 1991; **266**: 484-489 [PMID: 1845977]
- 11 Turinsky J, Bayly BP, O'Sullivan DM. 1,2-Diacylglycerol and ceramide levels in rat liver and skeletal muscle in vivo. *Am J Physiol* 1991; **261**: E620-E627 [PMID: 1951687]
- 12 Mazière C, Conte MA, Leborgne L, Levade T, Hornebeck W, Santus R, Mazière JC. UVA radiation stimulates ceramide production: relationship to oxidative stress and potential role in ERK, JNK, and p38 activation. *Biochem Biophys Res Commun* 2001; **281**: 289-294 [PMID: 11181043 DOI: 10.1006/bbrc.2001.4348]
- 13 Chang Y, Abe A, Shayman JA. Ceramide formation during heat shock: a potential mediator of  $\alpha$  B-crystallin transcription. *Proc Natl Acad Sci USA* 1995; **92**: 12275-12279 [PMID: 8618884]
- 14 Holland WL, Bikman BT, Wang LP, Yuguang G, Sargent KM, Bulchand S, Knotts TA, Shui G, Clegg DJ, Wenk MR, Pagliassotti MJ, Scherer PE, Summers SA. Lipid-induced insulin resistance mediated by the proinflammatory receptor TLR4 requires saturated fatty acid-induced ceramide biosynthesis in mice. *J Clin Invest* 2011; **121**: 1858-1870 [PMID: 21490391 DOI: 10.1172/JCI43378]
- 15 Taniguchi M, Kitatani K, Kondo T, Hashimoto-Nishimura M, Asano S, Hayashi A, Mitsutake S, Igarashi Y, Umehara H, Takeya H, Kigawa J, Okazaki T. Regulation of autophagy and its associated cell death by "sphingolipid rheostat": reciprocal role of ceramide and sphingosine 1-phosphate in the mammalian target of rapamycin pathway. *J Biol Chem* 2012; **287**: 39898-39910 [PMID: 23035115 DOI: 10.1074/jbc.M112.416552]
- 16 Obeid LM, Linardic CM, Karolak LA, Hannun YA. Programmed cell death induced by ceramide. *Science* 1993; **259**: 1769-1771 [PMID: 8456305]
- 17 Scarlatti F, Bauvy C, Ventruti A, Sala G, Cluzeaud F, Vande-walle A, Ghidoni R, Codogno P. Ceramide-mediated macroautophagy involves inhibition of protein kinase B and up-regulation of beclin 1. *J Biol Chem* 2004; **279**: 18384-18391 [PMID: 14970205 DOI: 10.1074/jbc.M313561200]
- 18 Wakita H, Tokura Y, Yagi H, Nishimura K, Furukawa F, Takigawa M. Keratinocyte differentiation is induced by cell-permeant ceramides and its proliferation is promoted by sphingosine. *Arch Dermatol Res* 1994; **286**: 350-354 [PMID: 7979551]
- 19 Summers SA, Garza LA, Zhou H, Birnbaum MJ. Regulation of insulin-stimulated glucose transporter GLUT4 translocation and Akt kinase activity by ceramide. *Mol Cell Biol* 1998; **18**: 5457-5464 [PMID: 9710629]
- 20 Adams JM, Pratipanawat T, Berria R, Wang E, DeFronzo RA, Sullards MC, Mandarino LJ. Ceramide content is increased in skeletal muscle from obese insulin-resistant humans. *Diabetes* 2004; **53**: 25-31 [PMID: 14693694]
- 21 Stratford S, Hoehn KL, Liu F, Summers SA. Regulation of insulin action by ceramide: dual mechanisms linking ceramide accumulation to the inhibition of Akt/protein kinase B. *J Biol Chem* 2004; **279**: 36608-36615 [PMID: 15220355 DOI: 10.1074/jbc.M406499200]
- 22 Arana L, Gangoiti P, Ouro A, Trueba M, Gómez-Muñoz A. Ceramide and ceramide 1-phosphate in health and disease. *Lipids Health Dis* 2010; **9**: 15 [PMID: 20137073 DOI: 10.1186/1476-511X-9-15]
- 23 Gangoiti P, Granado MH, Wang SW, Kong JY, Steinbrecher UP, Gómez-Muñoz A. Ceramide 1-phosphate stimulates macrophage proliferation through activation of the PI3-ki-

- nase/PKB, JNK and ERK1/2 pathways. *Cell Signal* 2008; **20**: 726-736 [PMID: 18234473 DOI: 10.1016/j.cellsig.2007.12.008]
- 24 **Gangoiti P**, Granado MH, Arana L, Ouro A, Gomez-Muñoz A. Activation of protein kinase C- $\alpha$  is essential for stimulation of cell proliferation by ceramide 1-phosphate. *FEBS Lett* 2010; **584**: 517-524 [PMID: 19948174 DOI: 10.1016/j.febslet.2009.11.086]
  - 25 **Suzuki E**, Handa K, Toledo MS, Hakomori S. Sphingosine-dependent apoptosis: a unified concept based on multiple mechanisms operating in concert. *Proc Natl Acad Sci USA* 2004; **101**: 14788-14793 [PMID: 15466700 DOI: 10.1073/pnas.0406536101]
  - 26 **Hannun YA**, Loomis CR, Merrill AH, Bell RM. Sphingosine inhibition of protein kinase C activity and of phorbol dibutyrate binding in vitro and in human platelets. *J Biol Chem* 1986; **261**: 12604-12609 [PMID: 3462188]
  - 27 **Ohta H**, Sweeney EA, Masamune A, Yatomi Y, Hakomori S, Igarashi Y. Induction of apoptosis by sphingosine in human leukemic HL-60 cells: a possible endogenous modulator of apoptotic DNA fragmentation occurring during phorbol ester-induced differentiation. *Cancer Res* 1995; **55**: 691-697 [PMID: 7834642]
  - 28 **McDonough PM**, Yasui K, Betto R, Salviati G, Glembocki CC, Palade PT, Sabbadini RA. Control of cardiac Ca<sup>2+</sup> levels. Inhibitory actions of sphingosine on Ca<sup>2+</sup> transients and L-type Ca<sup>2+</sup> channel conductance. *Circ Res* 1994; **75**: 981-989 [PMID: 7955152]
  - 29 **Smith ER**, Jones PL, Boss JM, Merrill AH. Changing J774A.1 cells to new medium perturbs multiple signaling pathways, including the modulation of protein kinase C by endogenous sphingoid bases. *J Biol Chem* 1997; **272**: 5640-5646 [PMID: 9038174]
  - 30 **Gomez-Muñoz A**, Hamza EH, Brindley DN. Effects of sphingosine, albumin and unsaturated fatty acids on the activation and translocation of phosphatidate phosphohydrolases in rat hepatocytes. *Biochim Biophys Acta* 1992; **1127**: 49-56 [PMID: 1320939 DOI: 10.1016/0005-2760(92)90200-F]
  - 31 **Jamal Z**, Martin A, Gomez-Muñoz A, Brindley DN. Plasma membrane fractions from rat liver contain a phosphatidate phosphohydrolase distinct from that in the endoplasmic reticulum and cytosol. *J Biol Chem* 1991; **266**: 2988-2996 [PMID: 1993672]
  - 32 **Natarajan V**, Jayaram HN, Scribner WM, Garcia JG. Activation of endothelial cell phospholipase D by sphingosine and sphingosine-1-phosphate. *Am J Respir Cell Mol Biol* 1994; **11**: 221-229 [PMID: 8049083]
  - 33 **Sakane F**, Yamada K, Kanoh H. Different effects of sphingosine, R59022 and anionic amphiphiles on two diacylglycerol kinase isozymes purified from porcine thymus cytosol. *FEBS Lett* 1989; **255**: 409-413 [PMID: 2551742 DOI: 10.1016/0014-5793(89)81134-2]
  - 34 **Yamada K**, Sakane F, Imai S, Takemura H. Sphingosine activates cellular diacylglycerol kinase in intact Jurkat cells, a human T-cell line. *Biochim Biophys Acta* 1993; **1169**: 217-224 [PMID: 7548113]
  - 35 **Vessey DA**, Li L, Kelley M, Zhang J, Karliner JS. Sphingosine can pre- and post-condition heart and utilizes a different mechanism from sphingosine 1-phosphate. *J Biochem Mol Toxicol* 2008; **22**: 113-118 [PMID: 18418901 DOI: 10.1002/jbt.20227]
  - 36 **Tao R**, Zhang J, Vessey DA, Honbo N, Karliner JS. Deletion of the sphingosine kinase-1 gene influences cell fate during hypoxia and glucose deprivation in adult mouse cardiomyocytes. *Cardiovasc Res* 2007; **74**: 56-63 [PMID: 17320845 DOI: 10.1016/j.cardiores.2007.01.015]
  - 37 **Tao R**, Hoover HE, Zhang J, Honbo N, Alano CC, Karliner JS. Cardiomyocyte S1P<sub>1</sub> receptor-mediated extracellular signal-related kinase signaling and desensitization. *J Cardiovasc Pharmacol* 2009; **53**: 486-494 [PMID: 19433984 DOI: 10.1097/FJC.0b013e3181a7b58a]
  - 38 **Pappu R**, Schwab SR, Cornelissen I, Pereira JP, Regard JB, Xu Y, Camerer E, Zheng YW, Huang Y, Cyster JG, Coughlin SR. Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. *Science* 2007; **316**: 295-298 [PMID: 17363629 DOI: 10.1126/science.1139221]
  - 39 **Chun J**, Goetzl EJ, Hla T, Igarashi Y, Lynch KR, Moolenaar W, Pyne S, Tigyi G. International Union of Pharmacology. XXXIV. Lysophospholipid receptor nomenclature. *Pharmacol Rev* 2002; **54**: 265-269 [PMID: 12037142]
  - 40 **Murata N**, Sato K, Kon J, Tomura H, Yanagita M, Kuwabara A, Ui M, Okajima F. Interaction of sphingosine 1-phosphate with plasma components, including lipoproteins, regulates the lipid receptor-mediated actions. *Biochem J* 2000; **352** Pt 3: 809-815 [PMID: 11104690]
  - 41 **Okajima F**. Plasma lipoproteins behave as carriers of extracellular sphingosine 1-phosphate: is this an atherogenic mediator or an anti-atherogenic mediator? *Biochim Biophys Acta* 2002; **1582**: 132-137 [PMID: 12069820 DOI: 10.1016/S1388-1981(02)00147-6]
  - 42 **Yatomi Y**, Ruan F, Hakomori S, Igarashi Y. Sphingosine-1-phosphate: a platelet-activating sphingolipid released from agonist-stimulated human platelets. *Blood* 1995; **86**: 193-202 [PMID: 7795224]
  - 43 **Schwab SR**, Pereira JP, Matloubian M, Xu Y, Huang Y, Cyster JG. Lymphocyte sequestration through S1P lyase inhibition and disruption of S1P gradients. *Science* 2005; **309**: 1735-1739 [PMID: 16151014 DOI: 10.1126/science.1113640]
  - 44 **Limaye V**, Li X, Hahn C, Xia P, Berndt MC, Vadas MA, Gamble JR. Sphingosine kinase-1 enhances endothelial cell survival through a PECAM-1-dependent activation of PI-3K/Akt and regulation of Bcl-2 family members. *Blood* 2005; **105**: 3169-3177 [PMID: 15632208 DOI: 10.1182/blood-2004-02-0452]
  - 45 **Kluk MJ**, Hla T. Signaling of sphingosine-1-phosphate via the S1P/EDG-family of G-protein-coupled receptors. *Biochim Biophys Acta* 2002; **1582**: 72-80 [PMID: 12069812 DOI: 10.1016/S1388-1981(02)00139-7]
  - 46 **Pébay A**, Toutant M, Prémont J, Calvo CF, Venance L, Cordier J, Glowinski J, Tencé M. Sphingosine-1-phosphate induces proliferation of astrocytes: regulation by intracellular signalling cascades. *Eur J Neurosci* 2001; **13**: 2067-2076 [PMID: 11467306]
  - 47 **Agudo-López A**, Miguel BG, Fernández I, Martínez AM. Involvement of mitochondria on neuroprotective effect of sphingosine-1-phosphate in cell death in an in vitro model of brain ischemia. *Neurosci Lett* 2010; **470**: 130-133 [PMID: 20045720 DOI: 10.1016/j.neulet.2009.12.070]
  - 48 **Kohama T**, Olivera A, Edsall L, Nagiec MM, Dickson R, Spiegel S. Molecular cloning and functional characterization of murine sphingosine kinase. *J Biol Chem* 1998; **273**: 23722-23728 [PMID: 9726979]
  - 49 **Mizugishi K**, Yamashita T, Olivera A, Miller GF, Spiegel S, Proia RL. Essential role for sphingosine kinases in neural and vascular development. *Mol Cell Biol* 2005; **25**: 11113-11121 [PMID: 16314531 DOI: 10.1128/MCB.25.24.11113-11121.2005]
  - 50 **Meyer zu Heringdorf D**, Lass H, Alemany R, Laser KT, Neumann E, Zhang C, Schmidt M, Rauen U, Jakobs KH, van Koppen CJ. Sphingosine kinase-mediated Ca<sup>2+</sup> signalling by G-protein-coupled receptors. *EMBO J* 1998; **17**: 2830-2837 [PMID: 9582276 DOI: 10.1093/emboj/17.10.2830]
  - 51 **Alemany R**, Meyer zu Heringdorf D, van Koppen CJ, Jakobs KH. Formyl peptide receptor signaling in HL-60 cells through sphingosine kinase. *J Biol Chem* 1999; **274**: 3994-3999 [PMID: 9933590]
  - 52 **Blaukat A**, Dikic I. Activation of sphingosine kinase by the bradykinin B2 receptor and its implication in regulation of the ERK/MAP kinase pathway. *Biol Chem* 2001; **382**: 135-139 [PMID: 11258664 DOI: 10.1515/BC.2001.020]
  - 53 **Young KW**, Bootman MD, Channing DR, Lipp P, Maycox PR, Meakin J, Challiss RA, Nahorski SR. Lysophospha-

- tidic acid-induced Ca<sup>2+</sup> mobilization requires intracellular sphingosine 1-phosphate production. Potential involvement of endogenous EDG-4 receptors. *J Biol Chem* 2000; **275**: 38532-38539 [PMID: 10954727 DOI: 10.1074/jbc.M006631200]
- 54 **Meyer zu Heringdorf D**, Lass H, Kuchar I, Lipinski M, Alemany R, Rümenapp U, Jakobs KH. Stimulation of intracellular sphingosine-1-phosphate production by G-protein-coupled sphingosine-1-phosphate receptors. *Eur J Pharmacol* 2001; **414**: 145-154 [PMID: 11239914 DOI: 10.1016/S0014-2999(01)00789-0]
- 55 **Olivera A**, Spiegel S. Sphingosine-1-phosphate as second messenger in cell proliferation induced by PDGF and FCS mitogens. *Nature* 1993; **365**: 557-560 [PMID: 8413613 DOI: 10.1038/365557a0]
- 56 **Meyer zu Heringdorf D**, Lass H, Kuchar I, Alemany R, Guo Y, Schmidt M, Jakobs KH. Role of sphingosine kinase in Ca(2+) signalling by epidermal growth factor receptor. *FEBS Lett* 1999; **461**: 217-222 [PMID: 10567700 DOI: 10.1016/S0014-5793(99)01463-5]
- 57 **Rius RA**, Edsall LC, Spiegel S. Activation of sphingosine kinase in pheochromocytoma PC12 neuronal cells in response to trophic factors. *FEBS Lett* 1997; **417**: 173-176 [PMID: 9395290 DOI: 10.1016/S0014-5793(97)01277-5]
- 58 **Shu X**, Wu W, Mosteller RD, Broek D. Sphingosine kinase mediates vascular endothelial growth factor-induced activation of ras and mitogen-activated protein kinases. *Mol Cell Biol* 2002; **22**: 7758-7768 [PMID: 12391145]
- 59 **Melendez A**, Floto RA, Gillooly DJ, Harnett MM, Allen JM. FcgammaRI coupling to phospholipase D initiates sphingosine kinase-mediated calcium mobilization and vesicular trafficking. *J Biol Chem* 1998; **273**: 9393-9402 [PMID: 9545263]
- 60 **Wang F**, Buckley NE, Olivera A, Goodemote KA, Su Y, Spiegel S. Involvement of sphingolipids metabolites in cellular proliferation modulated by ganglioside GM1. *Glycoconj J* 1996; **13**: 937-945 [PMID: 8981085]
- 61 **Sukocheva OA**, Wang L, Albanese N, Pitson SM, Vadas MA, Xia P. Sphingosine kinase transmits estrogen signaling in human breast cancer cells. *Mol Endocrinol* 2003; **17**: 2002-2012 [PMID: 12881510 DOI: 10.1210/me.2003-0119]
- 62 **Cavallini L**, Venerando R, Miotto G, Alexandre A. Ganglioside GM1 protection from apoptosis of rat heart fibroblasts. *Arch Biochem Biophys* 1999; **370**: 156-162 [PMID: 10510273 DOI: 10.1006/abbi.1999.1378]
- 63 **Pitson SM**, Moretti PA, Zebol JR, Lynn HE, Xia P, Vadas MA, Wattenberg BW. Activation of sphingosine kinase 1 by ERK1/2-mediated phosphorylation. *EMBO J* 2003; **22**: 5491-5500 [PMID: 14532121 DOI: 10.1093/emboj/cdg540]
- 64 **Pitson SM**, Moretti PA, Zebol JR, Xia P, Gamble JR, Vadas MA, D'Andrea RJ, Wattenberg BW. Expression of a catalytically inactive sphingosine kinase mutant blocks agonist-induced sphingosine kinase activation. A dominant-negative sphingosine kinase. *J Biol Chem* 2000; **275**: 33945-33950 [PMID: 10944534 DOI: 10.1074/jbc.M006176200]
- 65 **Leclercq TM**, Moretti PA, Vadas MA, Pitson SM. Eukaryotic elongation factor 1A interacts with sphingosine kinase and directly enhances its catalytic activity. *J Biol Chem* 2008; **283**: 9606-9614 [PMID: 18263879 DOI: 10.1074/jbc.M708782200]
- 66 **Kovanich D**, van der Heyden MA, Aye TT, van Veen TA, Heck AJ, Scholten A. Sphingosine kinase interacting protein is an A-kinase anchoring protein specific for type I cAMP-dependent protein kinase. *ChemBiochem* 2010; **11**: 963-971 [PMID: 20394097 DOI: 10.1002/cbic.201000058]
- 67 **Lacaná E**, Maceyka M, Milstien S, Spiegel S. Cloning and characterization of a protein kinase A anchoring protein (AKAP)-related protein that interacts with and regulates sphingosine kinase 1 activity. *J Biol Chem* 2002; **277**: 32947-32953 [PMID: 12080051 DOI: 10.1074/jbc.M202841200]
- 68 **Fukuda Y**, Aoyama Y, Wada A, Igarashi Y. Identification of PECAM-1 association with sphingosine kinase 1 and its regulation by agonist-induced phosphorylation. *Biochim Biophys Acta* 2004; **1636**: 12-21 [PMID: 14984734 DOI: 10.1016/j.bbaliip.2003.11.006]
- 69 **Hayashi H**, Nakagami H, Takami Y, Koriyama H, Mori M, Tamai K, Sun J, Nagao K, Morishita R, Kaneda Y. FHL-2 suppresses VEGF-induced phosphatidylinositol 3-kinase/Akt activation via interaction with sphingosine kinase-1. *Arterioscler Thromb Vasc Biol* 2009; **29**: 909-914 [PMID: 19325137 DOI: 10.1161/ATVBAHA.108.178541]
- 70 **Maceyka M**, Sankala H, Hait NC, Le Stunff H, Liu H, Toman R, Collier C, Zhang M, Satin LS, Merrill AH, Milstien S, Spiegel S. SphK1 and SphK2, sphingosine kinase isoenzymes with opposing functions in sphingolipid metabolism. *J Biol Chem* 2005; **280**: 37118-37129 [PMID: 16118219 DOI: 10.1074/jbc.M502207200]
- 71 **Karliner JS**. Sphingosine kinase and sphingosine 1-phosphate in cardioprotection. *J Cardiovasc Pharmacol* 2009; **53**: 189-197 [PMID: 19247197 DOI: 10.1097/FJC.0b013e3181926706]
- 72 **Igarashi N**, Okada T, Hayashi S, Fujita T, Jahangeer S, Nakamura S. Sphingosine kinase 2 is a nuclear protein and inhibits DNA synthesis. *J Biol Chem* 2003; **278**: 46832-46839 [PMID: 12954646 DOI: 10.1074/jbc.M306577200]
- 73 **Pfeilschifter W**, Czech-Zechmeister B, Sujak M, Mirceska A, Koch A, Rami A, Steinmetz H, Foerch C, Huwiler A, Pfeilschifter J. Activation of sphingosine kinase 2 is an endogenous protective mechanism in cerebral ischemia. *Biochem Biophys Res Commun* 2011; **413**: 212-217 [PMID: 21872577 DOI: 10.1016/j.bbrc.2011.08.070]
- 74 **Blondeau N**, Lai Y, Tyndall S, Popolo M, Topalkara K, Pru JK, Zhang L, Kim H, Liao JK, Ding K, Waeber C. Distribution of sphingosine kinase activity and mRNA in rodent brain. *J Neurochem* 2007; **103**: 509-517 [PMID: 17623044 DOI: 10.1111/j.1471-4159.2007.04755.x]
- 75 **Inagaki Y**, Li PY, Wada A, Mitsutake S, Igarashi Y. Identification of functional nuclear export sequences in human sphingosine kinase 1. *Biochem Biophys Res Commun* 2003; **311**: 168-173 [PMID: 14575709 DOI: 10.1016/j.bbrc.2003.09.194]
- 76 **Karliner JS**, Honbo N, Summers K, Gray MO, Goetzl EJ. The lysophospholipids sphingosine-1-phosphate and lysophosphatidic acid enhance survival during hypoxia in neonatal rat cardiac myocytes. *J Mol Cell Cardiol* 2001; **33**: 1713-1717 [PMID: 11549349 DOI: 10.1006/jmcc.2001.1429]
- 77 **Zhang J**, Honbo N, Goetzl EJ, Chatterjee K, Karliner JS, Gray MO. Signals from type 1 sphingosine 1-phosphate receptors enhance adult mouse cardiac myocyte survival during hypoxia. *Am J Physiol Heart Circ Physiol* 2007; **293**: H3150-H3158 [PMID: 17766476 DOI: 10.1152/ajpheart.00587.2006]
- 78 **Davis MD**, Clemens JJ, Macdonald TL, Lynch KR. Sphingosine 1-phosphate analogs as receptor antagonists. *J Biol Chem* 2005; **280**: 9833-9841 [PMID: 15590668 DOI: 10.1074/jbc.M412356200]
- 79 **Means CK**, Miyamoto S, Chun J, Brown JH. S1P1 receptor localization confers selectivity for Gi-mediated cAMP and contractile responses. *J Biol Chem* 2008; **283**: 11954-11963 [PMID: 18296752 DOI: 10.1074/jbc.M707422200]
- 80 **Means CK**, Xiao CY, Li Z, Zhang T, Omens JH, Ishii I, Chun J, Brown JH. Sphingosine 1-phosphate S1P2 and S1P3 receptor-mediated Akt activation protects against in vivo myocardial ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol* 2007; **292**: H2944-H2951 [PMID: 17293497 DOI: 10.1152/ajpheart.01331.2006]
- 81 **Ancellin N**, Colmont C, Su J, Li Q, Mittereder N, Chae SS, Stefansson S, Liao G, Hla T. Extracellular export of sphingosine kinase-1 enzyme. Sphingosine 1-phosphate generation and the induction of angiogenic vascular maturation. *J Biol Chem* 2002; **277**: 6667-6675 [PMID: 11741921 DOI: 10.1074/jbc.M102841200]
- 82 **Lee YM**, Venkataraman K, Hwang SI, Han DK, Hla T. A novel method to quantify sphingosine 1-phosphate by immobilized metal affinity chromatography (IMAC). *Prostaglandins Other Lipid Mediat* 2007; **84**: 154-162 [PMID: 17991617]

- DOI: 10.1016/j.prostaglandins.2007.08.001]
- 83 **Mungrue IN**, Zhao P, Yao Y, Meng H, Rau C, Havel JV, Gorgels TG, Bergen AA, MacLellan WR, Drake TA, Boström KI, Lusis AJ. Abcc6 deficiency causes increased infarct size and apoptosis in a mouse cardiac ischemia-reperfusion model. *Arterioscler Thromb Vasc Biol* 2011; **31**: 2806-2812 [PMID: 21979437 DOI: 10.1161/ATVBAHA.111.237420]
  - 84 **Solbach TF**, Paulus B, Weyand M, Eschenhagen T, Zolk O, Fromm MF. ATP-binding cassette transporters in human heart failure. *Naunyn Schmiedebergs Arch Pharmacol* 2008; **377**: 231-243 [PMID: 18392808 DOI: 10.1007/s00210-008-0279-6]
  - 85 **Hisano Y**, Kobayashi N, Kawahara A, Yamaguchi A, Nishi T. The sphingosine 1-phosphate transporter, SPNS2, functions as a transporter of the phosphorylated form of the immunomodulating agent FTY720. *J Biol Chem* 2011; **286**: 1758-1766 [PMID: 21084291 DOI: 10.1074/jbc.M110.171116]
  - 86 **Knapp M**, Zendzian-Piotrowska M, Kurek K, Błachnio-Zabielska A. Myocardial infarction changes sphingolipid metabolism in the uninfarcted ventricular wall of the rat. *Lipids* 2012; **47**: 847-853 [PMID: 22833182 DOI: 10.1007/s11745-012-3694-x]
  - 87 **Jin ZQ**, Zhou HZ, Zhu P, Honbo N, Mochly-Rosen D, Messing RO, Goetzl EJ, Karliner JS, Gray MO. Cardioprotection mediated by sphingosine-1-phosphate and ganglioside GM-1 in wild-type and PKC epsilon knockout mouse hearts. *Am J Physiol Heart Circ Physiol* 2002; **282**: H1970-H1977 [PMID: 12003800 DOI: 10.1152/ajpheart.01029.2001]
  - 88 **Lecour S**, Smith RM, Woodward B, Opie LH, Rochette L, Sack MN. Identification of a novel role for sphingolipid signaling in TNF alpha and ischemic preconditioning mediated cardioprotection. *J Mol Cell Cardiol* 2002; **34**: 509-518 [PMID: 12056855 DOI: 10.1006/jmcc.2002.1533]
  - 89 **Saurin AT**, Pennington DJ, Raat NJ, Latchman DS, Owen MJ, Marber MS. Targeted disruption of the protein kinase C epsilon gene abolishes the infarct size reduction that follows ischaemic preconditioning of isolated buffer-perfused mouse hearts. *Cardiovasc Res* 2002; **55**: 672-680 [PMID: 12160964 DOI: 10.1016/S0008-6363(02)00325-5]
  - 90 **Jin ZQ**, Goetzl EJ, Karliner JS. Sphingosine kinase activation mediates ischemic preconditioning in murine heart. *Circulation* 2004; **110**: 1980-1989 [PMID: 15451787 DOI: 10.1161/01.CIR.0000143632.06471.93]
  - 91 **Gray MO**, Zhou HZ, Schafhalter-Zoppoth I, Zhu P, Mochly-Rosen D, Messing RO. Preservation of base-line hemodynamic function and loss of inducible cardioprotection in adult mice lacking protein kinase C epsilon. *J Biol Chem* 2004; **279**: 3596-3604 [PMID: 14600145 DOI: 10.1074/jbc.M311459200]
  - 92 **Jin ZQ**, Karliner JS. Low dose N, N-dimethylsphingosine is cardioprotective and activates cytosolic sphingosine kinase by a PKCepsilon dependent mechanism. *Cardiovasc Res* 2006; **71**: 725-734 [PMID: 16831409 DOI: 10.1016/j.cardiores.2006.06.010]
  - 93 **Vessey DA**, Kelley M, Zhang J, Li L, Tao R, Karliner JS. Dimethylsphingosine and FTY720 inhibit the SK1 form but activate the SK2 form of sphingosine kinase from rat heart. *J Biochem Mol Toxicol* 2007; **21**: 273-279 [PMID: 17912702 DOI: 10.1002/jbt.20193]
  - 94 **Vessey DA**, Kelley M, Li L, Huang Y, Zhou HZ, Zhu BQ, Karliner JS. Role of sphingosine kinase activity in protection of heart against ischemia reperfusion injury. *Med Sci Monit* 2006; **12**: BR318-BR324 [PMID: 17006394]
  - 95 **Jin ZQ**, Zhang J, Huang Y, Hoover HE, Vessey DA, Karliner JS. A sphingosine kinase 1 mutation sensitizes the myocardium to ischemia/reperfusion injury. *Cardiovasc Res* 2007; **76**: 41-50 [PMID: 17610857 DOI: 10.1016/j.cardiores.2007.05.029]
  - 96 **Nishino Y**, Webb I, Marber MS. Sphingosine kinase isoforms and cardiac protection. *Cardiovasc Res* 2007; **76**: 3-4 [PMID: 17706621 DOI: 10.1016/j.cardiores.2007.07.007]
  - 97 **Vessey DA**, Li L, Jin ZQ, Kelley M, Honbo N, Zhang J, Karliner JS. A sphingosine kinase form 2 knockout sensitizes mouse myocardium to ischemia/reoxygenation injury and diminishes responsiveness to ischemic preconditioning. *Oxid Med Cell Longev* 2011; **2011**: 961059 [PMID: 21904650 DOI: 10.1155/2011/961059]
  - 98 **Zhao ZQ**, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen J. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 2003; **285**: H579-H588 [PMID: 12860564 DOI: 10.1152/ajp-heart.01064.2002]
  - 99 **Thibault H**, Piot C, Staat P, Bontemps L, Sportouch C, Rioufol G, Cung TT, Bonnefoy E, Angoulvant D, Aupetit JF, Finet G, André-Fouët X, Macia JC, Raczka F, Rossi R, Itti R, Kirkorian G, Derumeaux G, Ovize M. Long-term benefit of postconditioning. *Circulation* 2008; **117**: 1037-1044 [PMID: 18268150 DOI: 10.1161/CIRCULATIONAHA.107.729780]
  - 100 **Jin ZQ**, Karliner JS, Vessey DA. Ischaemic postconditioning protects isolated mouse hearts against ischaemia/reperfusion injury via sphingosine kinase isoform-1 activation. *Cardiovasc Res* 2008; **79**: 134-140 [PMID: 18334546 DOI: 10.1093/cvr/cvn065]
  - 101 **Vessey DA**, Li L, Kelley M, Karliner JS. Combined sphingosine, S1P and ischemic postconditioning rescue the heart after protracted ischemia. *Biochem Biophys Res Commun* 2008; **375**: 425-429 [PMID: 18706887 DOI: 10.1016/j.bbrc.2008.08.022]
  - 102 **Salomone S**, Potts EM, Tyndall S, Ip PC, Chun J, Brinkmann V, Waeber C. Analysis of sphingosine 1-phosphate receptors involved in constriction of isolated cerebral arteries with receptor null mice and pharmacological tools. *Br J Pharmacol* 2008; **153**: 140-147 [PMID: 18026125 DOI: 10.1038/sj.bjp.0707581]
  - 103 **Matloubian M**, Lo CG, Cinamon G, Lesneski MJ, Xu Y, Brinkmann V, Allende ML, Proia RL, Cyster JG. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* 2004; **427**: 355-360 [PMID: 14737169 DOI: 10.1038/nature02284]
  - 104 **Kimura A**, Ohmori T, Kashiwakura Y, Ohkawa R, Madoiwa S, Mimuro J, Shimazaki K, Hoshino Y, Yatomi Y, Sakata Y. Antagonism of sphingosine 1-phosphate receptor-2 enhances migration of neural progenitor cells toward an area of brain. *Stroke* 2008; **39**: 3411-3417 [PMID: 18757288 DOI: 10.1161/STROKEAHA.108.514612]
  - 105 **Wacker BK**, Freie AB, Perfater JL, Gidday JM. Junctional protein regulation by sphingosine kinase 2 contributes to blood-brain barrier protection in hypoxic preconditioning-induced cerebral ischemic tolerance. *J Cereb Blood Flow Metab* 2012; **32**: 1014-1023 [PMID: 22314269 DOI: 10.1038/jcbfm.2012.3]
  - 106 **Yung LM**, Wei Y, Qin T, Wang Y, Smith CD, Waeber C. Sphingosine kinase 2 mediates cerebral preconditioning and protects the mouse brain against ischemic injury. *Stroke* 2012; **43**: 199-204 [PMID: 21980199 DOI: 10.1161/STROKEAHA.111.626911]
  - 107 **Zhou Y**, Lekic T, Fathali N, Ostrowski RP, Martin RD, Tang J, Zhang JH. Isoflurane posttreatment reduces neonatal hypoxic-ischemic brain injury in rats by the sphingosine-1-phosphate/phosphatidylinositol-3-kinase/Akt pathway. *Stroke* 2010; **41**: 1521-1527 [PMID: 20508187 DOI: 10.1161/STROKEAHA.110.583757]
  - 108 **Wacker BK**, Park TS, Gidday JM. Hypoxic preconditioning-induced cerebral ischemic tolerance: role of microvascular sphingosine kinase 2. *Stroke* 2009; **40**: 3342-3348 [PMID: 19644058 DOI: 10.1161/STROKEAHA.109.560714]
  - 109 **Baumruker T**, Billich A, Brinkmann V. FTY720, an immunomodulatory sphingolipid mimetic: translation of a novel mechanism into clinical benefit in multiple sclerosis. *Expert Opin Investig Drugs* 2007; **16**: 283-289 [PMID: 17302523 DOI: 10.1517/13543784.16.3.283]
  - 110 **Pelletier D**, Hafler DA. Fingolimod for multiple sclerosis. *N Engl J Med* 2012; **366**: 339-347 [PMID: 22276823 DOI: 10.1056/NEJMc1101691]

- 111 **Billich A**, Bornancin F, Dévay P, Mechtcheriakova D, Urtz N, Baumruker T. Phosphorylation of the immunomodulatory drug FTY720 by sphingosine kinases. *J Biol Chem* 2003; **278**: 47408-47415 [PMID: 13129923 DOI: 10.1074/jbc.M307687200]
- 112 **Brinkmann V**, Davis MD, Heise CE, Albert R, Cottens S, Hof R, Bruns C, Prieschl E, Baumruker T, Hiestand P, Foster CA, Zollinger M, Lynch KR. The immune modulator FTY720 targets sphingosine 1-phosphate receptors. *J Biol Chem* 2002; **277**: 21453-21457 [PMID: 11967257 DOI: 10.1074/jbc.C200176200]
- 113 **Hasegawa Y**, Suzuki H, Sozen T, Rolland W, Zhang JH. Activation of sphingosine 1-phosphate receptor-1 by FTY720 is neuroprotective after ischemic stroke in rats. *Stroke* 2010; **41**: 368-374 [PMID: 19940275 DOI: 10.1161/STROKEAHA.109.568899]
- 114 **Czech B**, Pfeilschifter W, Mazaheri-Omrani N, Strobel MA, Kahles T, Neumann-Haefelin T, Rami A, Huwiler A, Pfeilschifter J. The immunomodulatory sphingosine 1-phosphate analog FTY720 reduces lesion size and improves neurological outcome in a mouse model of cerebral ischemia. *Biochem Biophys Res Commun* 2009; **389**: 251-256 [PMID: 19720050 DOI: 10.1016/j.bbrc.2009.08.142]
- 115 **Wei Y**, Yemisci M, Kim HH, Yung LM, Shin HK, Hwang SK, Guo S, Qin T, Alsharif N, Brinkmann V, Liao JK, Lo EH, Waeber C. Fingolimod provides long-term protection in rodent models of cerebral ischemia. *Ann Neurol* 2011; **69**: 119-129 [PMID: 21280082 DOI: 10.1002/ana.22186]
- 116 **Brinkmann V**, Pinschewer DD, Feng L, Chen S. FTY720: altered lymphocyte traffic results in allograft protection. *Transplantation* 2001; **72**: 764-769 [PMID: 11571432]
- 117 **Jung CG**, Kim HJ, Miron VE, Cook S, Kennedy TE, Foster CA, Antel JP, Soliven B. Functional consequences of S1P receptor modulation in rat oligodendroglial lineage cells. *Glia* 2007; **55**: 1656-1667 [PMID: 17876806 DOI: 10.1002/glia.20576]
- 118 **Stessin AM**, Gursel DB, Schwartz A, Parashar B, Kulidzhianov FG, Sabbas AM, Boockvar J, Nori D, Wernicke AG. FTY720, sphingosine 1-phosphate receptor modulator, selectively radioprotects hippocampal neural stem cells. *Neurosci Lett* 2012; **516**: 253-258 [PMID: 22507238 DOI: 10.1016/j.neulet.2012.04.004]
- 119 **Yagi H**, Kamba R, Chiba K, Soga H, Yaguchi K, Nakamura M, Itoh T. Immunosuppressant FTY720 inhibits thymocyte emigration. *Eur J Immunol* 2000; **30**: 1435-1444 [PMID: 10820391]
- 120 **Liesz A**, Sun L, Zhou W, Schwarting S, Mracsko E, Zorn M, Bauer H, Sommer C, Veltkamp R. FTY720 reduces post-ischemic brain lymphocyte influx but does not improve outcome in permanent murine cerebral ischemia. *PLoS One* 2011; **6**: e21312 [PMID: 21701599 DOI: 10.1371/journal.pone.0021312]
- 121 **Liu J**, Zhang C, Tao W, Liu M. Systematic review and meta-analysis of the efficacy of sphingosine-1-phosphate (S1P) receptor agonist FTY720 (fingolimod) in animal models of stroke. *Int J Neurosci* 2013; **123**: 163-169 [PMID: 23167788 DOI: 10.3109/00207454.2012.749255]

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## Drugs to be avoided in patients with long QT syndrome: Focus on the anaesthesiological management

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**Key words:** Long QT Syndrome; Torsades de pointes; Anesthesia; QT-prolongation; Anesthetic drugs

**Core tip:** Long QT syndrome is a cardiac conduction disorder characterized by prolongation and increased dispersion of ventricular repolarization, manifested by lengthening of the QT interval on the surface electrocardiography. This review furnishes important key points for preoperative optimization, intraoperative anesthetic agents and postoperative care in order to fill the lack of definitive guidelines on anesthetic management of c-long QT syndrome.

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### Abstract

Long QT syndrome incidence is increasing in general population. A careful pre-, peri- and post-operative management is needed for patients with this syndrome because of the risk of Torsades de Pointes and malignant arrhythmias. The available data regarding prevention of lethal Torsades de Pointes during anesthesia in patients with long QT syndrome is scant and conflicting: only case reports and small case series with different outcomes have been published. Actually, there are no definitive guidelines on pre-, peri- and post-operative anesthetic management of congenital long QT syndrome. Our review focuses on anesthetic recommendations for patients diagnosed with congenital long QT syndrome furnishing some key points for preoperative optimization, intraoperative anesthetic agents and post-operative care plan, which could be the best for patients with c-long QT syndrome who undergo surgery.

### INTRODUCTION

Long QT syndrome (LQTS) is a cardiac conduction disorder characterized by prolongation and increased dispersion of ventricular repolarization, manifested by lengthening of the QT interval on the surface electrocardiography (ECG). This abnormal repolarization, when amplified by sympathetic activity, can lead to the formation of reentry circuits and may present with syncope, seizures, or torsades de pointes (TdP), ventricular fibrillation and, therefore sudden cardiac death<sup>[1]</sup>. Moreover, there are other signs of the torsadogenic property of a drug: QT dispersion (difference between the longest and the shortest QT interval) and the transmural dispersion of repolarization (TDR) (time between the peak and the end of the T wave in a precordial lead)<sup>[2]</sup>. Traditionally, LQTS is divided into congenital (c-LQTS) and acquired

(a-LQTS) forms. Drug-induced LQTS is the most common cause of a-LQTS; as a matter of fact, a survey by Schwartz *et al.*<sup>[3]</sup> of 670 patients in the International LQTS Registry revealed that anesthesia can trigger LQTS.

Ninety-five percent of drug-induced LQTS is due to the obstruction of the rapid component of the late correcting potassium current ( $I_{Kr}$ ), which physiologically allows the rapid potassium outflow<sup>[4]</sup>.  $I_{Kr}$  and the slow component of the same channel ( $I_{Ks}$ ) are responsible for the repolarization of cardiomyocytes. Some anesthetics and some drugs used in premedication may lead to QT-prolongation. The available data on the prevention of lethal TdP during anesthesia in patients with c-LQTS is scant and conflicting: only case reports and small case series with different outcomes, even when using the same anesthetic agent, have been published<sup>[2,5-19]</sup>. Although a-LQTS is of significant interest, this review focuses on the anesthetic recommendations for patients diagnosed with c-LQTS. Our aim is to provide some key points which could help both the cardiologists and the anesthesiologists when approaching a patient with LQTS candidate for anaesthesiological procedures. Firstly, we describe which drugs should be avoided in LQTS and then we move on the specific topic of the review describing the anaesthesiological management of patients with LQTS.

## DRUGS TO BE AVOIDED IN LQTS

Certain drugs, including some anesthetics, are known to contribute to QT prolongation. Considering that not all agents that prolong the QT interval increase TDR, drugs can be distinguished into the following groups depending on their simultaneous effects on the QT corrected using the Bazett's formula ( $QT_c$ ) interval and on TDR<sup>[20]</sup>: (1) drugs inducing both  $QT_c$  prolongation and increased TDR, characterized by a high torsadogenic potential; (2) drugs causing  $QT_c$  prolongation but with a slight effect on TDR and little, if any, ability to induce TdP; and (3) drugs causing both  $QT_c$  prolongation and increased TDR below a certain concentration, but inducing TdP once a critical value of TDR is exceeded.

Drugs that prolong the QT interval and/or induce Torsades de Pointes in patients with diagnosed or suspected c-LQTS are shown on Table 1<sup>[21]</sup> and can be found on the web pages [www.torsades.org](http://www.torsades.org). Some of these drugs are not available in every country (many of them have been withdrawn from the market in several countries). However, this list doesn't include some anesthetic agents which have an influence on cardiac conduction and can lead to intraoperative TdP; hence, they are discussed throughout the text.

## ANAESTHETICS IN LQTS

Despite an adequate  $\beta$ -blocking, patients with LQTS candidate to surgical or anesthetic procedure have an increased risk of developing perioperative ventricular arrhythmias. The probability of developing these arrhyth-

mias significantly decreases with a careful pre-, intra- and post-operative management.

### Preoperative management

A good anaesthesiological preoperative physical examination should be the cornerstone, mostly in childhood and adolescence. Moreover, an ECG at rest is always needed in order to reveal a QT prolongation. Patients treated with beta-blockers should continue their medication throughout the perioperative period until the operating day. Electrolytes should be normalized. Drugs known to induce TdP (Table 1) should be discontinued or the dose should be decreased if it cannot be discontinued. The presence of a pacemaker or implantable cardioverter defibrillator should be checked.

### Perioperative management

Some anesthetics and some drugs used for premedication may lead to QT-prolongation. The torsadogenic effect is related both to the drug and to the anaesthesiological and surgical manoeuvres.

### Drugs used for premedication and sedation

Since anxiety and pain can trigger arrhythmias in patients with LQTS, pre-anesthetic medication is recommended. Anesthetic premedication is usually performed using vagolytic and sedative/analgesic drugs. Among these drugs, atropine causes a lengthening of the QT interval and should not be used<sup>[22]</sup>. On the other hand many studies demonstrated that midazolam does not modify either  $QT_c$  or TDR<sup>[23,24]</sup>; hence, it should be used for premedication in patients with c-LQTS. Midazolam reduces sympathetic activity in unstimulated patients but it does not blunt the hemodynamic response to oral or nasal intubation<sup>[23]</sup>. Few authors verified the utility of different drugs to prevent lengthening of  $QT_c$  interval associated to intubation: Owczuk *et al.*<sup>[25]</sup> demonstrated that the use of intravenous lidocaine (1.5 mg/kg) before laryngoscopy and intubation prevented prolongation of the  $QT_c$  interval induced by the maneuver. Therefore, it seems useful the association of midazolam in premedication and lidocaine before intubation.

Droperidol, used for neuroleptanalgesia in intensive-care treatment since 1970, extends the  $QT_c$  interval by the  $I_{Kr}$  current blockade through the HERG channel; because of this effect on  $QT_c$  this drug was withdrawn from the market in 2001<sup>[26,27]</sup>. This decision was focus of debate; hence, the drug was licensed again in 2008 and it is used in premedication both for sedation and antiemetic treatment<sup>[28-31]</sup>. However, Staikou *et al.*<sup>[32]</sup> advise against the use of droperidol in patients with LQTS in a recent review.

Lastly, an adequate sedoanalgesia reduces catecholamine release; the most used drugs are morphine, meperidin and fentanyl. Though the effects of fentanyl on  $QT_c$  interval are conflicting, fentanyl and morphine have been used in patients with c-LQTS without any adverse effect<sup>[17,33-36]</sup>. On the other hand, Song *et al.*<sup>[37]</sup> recently re-

**Table 1** Drugs that prolong the QT interval and/or induce torsades de pointes

Drugs to be avoided in patients with c-long QT syndrome		
Class		Generic name
Anesthetic		Sevoflurane
Anti-anginal		Ranolazine, Bepridil
Anti-arrhythmic	Sotalol, Quinidine, Amiodarone, Ibutilide, Disopyramide, Procainamide, Flecainide, Dofetilide, Dronedarone	
Antibiotic	Moxifloxacin, Clarithromycin, Ciprofloxacin, Gemifloxacin, Ofloxacin Telithromycin, Levofloxacin, Roxithromycin, Trimethoprim-Sulfa, Gatifloxacin, Sparfloxacin, Azithromycin Erythromycin	
Anti-cancer	Tamoxifen, Lapatinib, Nilotinib, Arsenic trioxide, Eribulin, Sunitinib	
Anti-convulsant		Vandetanib
Anti-depressant	Mirtazapine, Citalopram, Venlafaxine, Paroxetine, Fluoxetine, Sertraline, Trazodone, Escitalopram, Clomipramine, Amitriptyline, Imipramine, Nortriptyline, Desipramine, Doxepin, Trimipramine, Protriptyline	
Anti-fungal		Voriconazole, Fluconazole, Ketoconazole, Itraconazole
Antihistamine		Astemizole, Terfenadine, Diphenhydramine, Diphenhydramine
Anti-hypertensive		Nicardipine, Isradipine, Moexipril/HCTZ
Anti-infective		Pentamidine
Antilipemic		Probucol
Anti-malarial		Arteminol + piperazine, Chloroquine, Halofantrine
Anti-mania		Lithium
Anti-nausea/antiemetic		Granisetron, Dolasetron, Ondansetron
Anti-psychotic	Clozapine, Ziprasidone, Thioridazine, Risperidone, Mesoridazine, Quetiapine, Haloperidol, Pimozide, Amisulpride, Sertindole, Sertindole, Iloperidone, Paliperidone, Chlorpromazine	
Anti-viral		Foscarnet, Ritonavir, Atazanavir
Appetite suppressant		Phentermine, Fenfluramine, Sibutramine
Bladder Antispasmodic		Tolterodine
$\alpha$ 1-blocker		Alfuzosin
Bronchodilator/decongestant	Albuterol, Salmeterol, Metaproterenol, Terbutaline, Metaproterenol, Levalbuterol, Ephedrine, Phenylpropanolamine, Pseudoephedrine	
Cholinesterase inhibitor		Galantamine
CNS stimulant		Amphetamine
		Methylphenidate
		Amphetamine
		Dexamethylphenidate
		Methylphenidate
		Lisdexamfetamine
		Indapamide
Diuretic		Amantadine
Dopaminergic/anti-viral/anti-infective/		Ocreotide
Endocrine		Cisapride
GI stimulant		Famotidine
H2-receptor antagonist		Perflutren lipid microspheres
Imaging contrast agent		Tacrolimus, Fingolimod
Immunosuppressant		
Inotropic agent/vasconstrictor	Dopamine, Isoproterenol, Dobutamine, Epinephrine, Norepinephrine, Phenylephrine	
Local anesthetic		Cocaine
Muscarinic receptor antagonist		Solifenacin
Muscle relaxant		Tizanidine
norepinephrine reuptake inhibitor		Atomoxetine
Opiate agonist		Methadone, Levomethadyl
Oxytocic		Oxytocin
phosphodiesterase inhibitor/vasodilator		Vardenafil
Sedative		Chloral hydrate
Sedative; Anti-nausea/anaesthesia adjunct		Droperidol
Uterine relaxant		Ritodrine
Vasconstrictor		Midodrine

A continuously updated list of these drugs is available at [www.torsades.org](http://www.torsades.org) (accessed December 16, 2012). CNS: Central Nervous System.

ported that the intravenous injection of meperidine led to QTc prolongation, polymorphic ventricular tachycardia and ventricular fibrillation, in a 16-year-old boy without neither underlying cardiac disease nor mutation in *LQTS* genes, but with a single nucleotide polymorphism, including H558R in *SCN5A* and K897T in *KCNH2*. Alfentanil does not extend repolarization time<sup>[2]</sup>. On the

contrary, sufentanil prolongs QTc interval<sup>[38]</sup>.

### General anesthesia

**Induction and maintenance:** Induction of anesthesia can be done using halogenated volatile anesthetics or using intravenous agents, which are distinguished in barbiturates (sodium thiopental) and non barbiturates

**Table 2** Normal QT corrected using the Bazett's formula duration by age and gender

QT corrected using the Bazett's formula			
QTc value (s)	Children (1-15 yr)	Male ( > 15 yr)	Female ( > 15 yr)
Normal	< 0.44	< 0.43	< 0.45
Borderline	0.44-0.46	0.43-0.45	0.45-0.46
Prolonged	> 0.46	> 0.45	> 0.46

QTc: QT corrected using the Bazett's formula.

(Propofol or Ketamine). Maintenance of anesthesia is usually achieved by allowing the patient to breathe a carefully controlled mixture of oxygen, nitrous oxide, and a volatile anaesthetic agent or by having a total intravenous anesthesia (TIVA) using intravenous agents in infusion together with analgesia.

Halogenated volatile anesthetics (Halothane, Enflurane, Isoflurane, Desflurane and Sevoflurane) prolong the QTc interval, even if data is controversial for some of them<sup>[39-43]</sup>. Isoflurane has been used safely in patients with LQTS<sup>[13,44]</sup>. Sevoflurane produced significant arrhythmias in a pediatric patient with c-LQTS<sup>[10]</sup>; moreover, it causes lengthening of QTc interval both in young and adults<sup>[5,45-49]</sup>. The clinical significance of these findings in patients with LQTS is unclear<sup>[50]</sup>, but it is recommended to avoid these agents.

Thiopental (sodium thiopental) has been used safely in patients with c-LQTS even if it causes QTc prolongation in humans<sup>[13,51-53]</sup>. Thiopental may reduce TDR through a longer prolongation of the action potential duration in endocardial and epicardial cells compared to M-cell and theoretically it could prevent the spontaneous onset of TdP<sup>[51,54]</sup>.

Data about the effect of Propofol on QTc is conflicting, while we certainly know that this drug does not modify TDR<sup>[55-58]</sup>. Moreover, Propofol rapidly reverses Sevoflurane-induced QTc prolongation in healthy patients and therefore may be beneficial<sup>[59]</sup>. Although Ketamine was used in premedication in children with undiagnosed c-LQTS, it is not recommended in patients with LQTS because its sympathomimetic properties can favor incidents of TdP<sup>[51]</sup>. Etomidate does not affect the duration of ventricular repolarization<sup>[25,60]</sup>. However, Erdil *et al*<sup>[61]</sup> compared the effect of Propofol and Etomidate during electroconvulsive therapy, which may cause an acute rise in QT dispersion, and they found out that Etomidate increased QT more than Propofol.

### Anesthesiologic maneuvers

**Intubation and extubation:** Usually the prophylactic administration of muscle relaxants eases intubation. Succinylcholine has been used in some patients with c-LQTS but it may either prolongs the QT interval in patients with c-LQTS, especially during tracheal intubation, or determine a vagal stimulation or result in asystole after pacemaker inhibition by fasciculations; for these reasons it should be avoided<sup>[19,22,62-64]</sup>. The effects of succinylcho-

line on QTc can be reversed by alfentanil; the same is not possible with fentanyl<sup>[65]</sup>. Moreover, alfentanil was better than esmolol in preventing the increase in QTc induced by succinylcholine during tracheal intubation<sup>[66]</sup>. Rocuronium, vecuronium, atracurium, and cisatracurium do not extend the QTc interval and can be used in c-LQTS, while pancuronium should be avoided because of its vagolytic properties and because it caused ventricular fibrillation in a case report<sup>[14,23,35,51,52]</sup>.

Both intubation and extubation may trigger a TdP in patients with c-LQTS: hence, additional care should be taken during these maneuvers and analgesic or beta-blockers should be administered before them. As aforementioned, the use of lidocaine before intubation proved to be safe to prevent arrhythmias<sup>[25]</sup>. Finally, during ventilation with positive pressure, anesthesiologists should avoid high inspiratory pressure peaks and wide inspiratory/expiratory ratios, since the Valsalva maneuver also prolongs the QTc interval<sup>[65]</sup>.

### Postoperative management

Postoperative management of patients with c-LQTS should include the permanence in a postsurgical intensive care unit for at least 24 h, avoiding stimuli that could trigger TdP. An adequate postoperative analgesia and beta-blocking must be guaranteed. Postoperative nausea and vomiting (PONV) prevention can not be performed with setrones (ondansetron, granisetron and dolasetron) in patients with c-LQTS because these drugs block not only the 5HT<sub>3</sub> receptors but also the HERG channel, determining a prolongation of repolarization. A study by Charbit *et al*<sup>[67]</sup> demonstrated that 4 mg of ondansetron induced prolongation of the QTc, similar to the effect of 0.75 mg of droperidol, therefore questioning the greater safety of ondansetron when compared to droperidol in the treatment of PONV; Accordingly Staikou *et al*<sup>[32]</sup> advise against its use in patients with c-LQTS.

## CONCLUSION

The prevalence of Long QT syndrome is close to 1/3000-1/5000<sup>[68,69]</sup>. The QT interval duration is physiologically variable: the QTc is calculated using the Bazett's formula  $[(QTc = QT/\sqrt{RR})]$ , Table 2<sup>[70,71]</sup>. Genetic testing can help to recognize specific subtypes of c-LQTS. The most common phenotypes are LQT1, LQT2 and LQT3. People with LQT1, the most common variant of LQTS, are more likely to have a cardiac event during exercise than patients with LQT2 or LQT3. LQT1 is associated with a mutation in the *KvLQT1* gene (also known as *KCNQ1*), which codes for a protein that co-assembles with another protein (minK) to form the *I<sub>K-s</sub>*<sup>[72]</sup>. In patients with LQT2 arrhythmic events are usually triggered by auditory stimuli or sudden startle<sup>[73]</sup>. LQT2 is caused by the loss of *I<sub>Kr</sub>*<sup>[72]</sup>. Patients with LQT3 are prone to syncope or cardiac arrest at rest or during sleep; as a matter of fact, their electrocardiographic abnormalities become less marked at increased heart rate<sup>[72,74]</sup>. Table

**Table 3** Electrocardiograph pattern in long QT syndrome

ECG in LQTS	
LQT1	Prolonged QT, T wave normal or with increased amplitude with a wide base
LQT2	Prolonged QT, T wave with low amplitude and often bifid
LQT3	Late onset of the T wave, prolonged isoelectric segment

ECG: Electrocardiography; LQTS: Long QT syndrome.

3 shows the electrocardiographic patterns of the most common phenotypes of LQTS. Both in the a-LQTS and in the c-LQTS, the blockade of ionic channels, the lengthening of the QT interval and the intensification of QTD can provoke the induction of TdP<sup>[75]</sup>. A careful pre-, peri- and post-operative management is needed for patients with this syndrome because of the risk of TdP and malignant arrhythmias. We speculate that genetic subtyping of patients with LQTS could help tailor anesthetic therapy for these high-risk patients.

Actually, there are no definitive guidelines for pre-, peri- and post-operative anesthetic management of c-LQTS. After reviewing the literature, we furnish some key points for preoperative optimization, intraoperative anesthetic agents and postoperative care plan that may be the best for patients with c-LQTS who undergo surgery. In the preoperative period it is necessary to calculate QTc, perform a 12-lead ECG at rest, discontinue or decrease the dose of drugs which could increase QTc interval and trigger a TdP in these patients (Table 1), continue beta-blocking therapy until the operating day and maintain calm and quiet environment. Defibrillator must be available for immediate use during the perioperative period.

In the perioperative period, it would be better to do premedication with midazolam, sedoanalgesia with morphine or fentanyl, induction and maintenance of anesthesia with thiopental or propofol TIVA avoiding halogenated volatile anesthetics and ketamine. Before intubation and extubation, the use of a topic anesthetic, an analgesic or a beta-blocker could be recommended. Among muscle relaxant drugs, we should prefer vecuronium and atracurium. It is important to monitor not only heart rate, blood pressure, oximetry, capnometry but also ECG in at least two leads, as short episodes of TdP are hardly distinguished from monomorphic VT, when traced in one lead. In the postoperative the patient must be monitored and ECG should last until patient emerges from anesthesia and QTc turns into preoperative values. Any kind of stimulus should be avoided since they could trigger TdP and pain must be adequately controlled.

## REFERENCES

- Schwartz PJ**, Priori SG, Napolitano C. The long QT syndrome. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. 3rd ed. Philadelphia: WB Saunders, 2000: 597-615
- Owczuk R**, Wujewicz MA, Ziencuk-Krajka A, Lasińska-Kowara M, Piankowski A, Wujewicz M. The influence of anesthesia on cardiac repolarization. *Minerva Anesthesiol* 2012; **78**: 483-495 [PMID: 22318402]
- Schwartz PJ**, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001; **103**: 89-95 [PMID: 11136691 DOI: 10.1161/01.CIR.103.1.89]
- De Bruin ML**, Pettersson M, Meyboom RH, Hoes AW, Leufkens HG. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. *Eur Heart J* 2005; **26**: 590-597 [PMID: 15637086 DOI: 10.1093/eurheartj/ehi092]
- Tacke MC**, Bracke FA, Van Zundert AA. Torsade de pointes during sevoflurane anesthesia and fluconazole infusion in a patient with long QT syndrome. A case report. *Acta Anaesthesiol Belg* 2011; **62**: 105-108 [PMID: 21919379]
- Mandal B**, Kaur G, Batra YK, Mahajan S. Manifestation of Long QT syndrome with normal QTc interval under anesthesia: a case report. *Paediatr Anaesth* 2011; **21**: 1265-1267 [PMID: 21824216 DOI: 10.1111/j.1460-9592.2011.03679.x]
- Kim HT**, Lee JH, Park IB, Heo HE, Kim TY, Lee MJ. Long QT syndrome provoked by induction of general anesthesia -A case report-. *Korean J Anesthesiol* 2010; **59** Suppl: S114-S118 [PMID: 21286418 DOI: 10.4097/kjae.2010.59.S114]
- Komarlu R**, Beerman L, Freeman D, Arora G. Fetal and neonatal presentation of long QT syndrome. *Pacing Clin Electrophysiol* 2012; **35**: e87-e90 [PMID: 21401653 DOI: 10.1111/j.1540-8159.2011.03040.x]
- Thiruvengatarajan V**, Osborn KD, Van Wijk RM, Euler P, Sethi R, Moodie S, Biradar V. Torsade de pointes in a patient with acute prolonged QT syndrome and poorly controlled diabetes during sevoflurane anaesthesia. *Anaesth Intensive Care* 2010; **38**: 555-559 [PMID: 20514968]
- Kenyon CA**, Flick R, Moir C, Ackerman MJ, Pabelick CM. Anesthesia for videoscopic left cardiac sympathetic denervation in children with congenital long QT syndrome and catecholaminergic polymorphic ventricular tachycardia--a case series. *Paediatr Anaesth* 2010; **20**: 465-470 [PMID: 20337957 DOI: 10.1111/j.1460-9592.2010.03293.x]
- Lin MT**, Wu MH, Chang CC, Chiu SN, Thériault O, Huang H, Christé G, Ficker E, Chahine M. In utero onset of long QT syndrome with atrioventricular block and spontaneous or lidocaine-induced ventricular tachycardia: compound effects of hERG pore region mutation and SCN5A N-terminus variant. *Heart Rhythm* 2008; **5**: 1567-1574 [PMID: 18848812 DOI: 10.1016/j.hrthm.2008.08.010]
- Femenia F**, Ruiz-Gimeno JL, Ferre MA, Cabezudo L, Vivó C, Barberá M. [Total intravenous anesthesia for repositioning an implantable defibrillator in a patient with long QT syndrome]. *Rev Esp Anesthesiol Reanim* 2008; **55**: 367-370 [PMID: 18693663]
- Johnston AJ**, Hall JM, Levy DM. Anaesthesia with remifentanyl and rocuronium for caesarean section in a patient with long-QT syndrome and an automatic implantable cardioverter-defibrillator. *Int J Obstet Anesth* 2000; **9**: 133-136 [PMID: 15321099 DOI: 10.1054/ijoa.1999.0362]
- Al-Refai A**, Gunka V, Douglas J. Spinal anesthesia for Cesarean section in a parturient with long QT syndrome. *Can J Anaesth* 2004; **51**: 993-996 [PMID: 15574549]
- Pleym H**, Bathen J, Spigset O, Gisvold SE. Ventricular fibrillation related to reversal of the neuromuscular blockade in a patient with long QT syndrome. *Acta Anaesthesiol Scand* 1999; **43**: 352-355 [PMID: 10081545 DOI: 10.1034/j.1399-6576.1999.430319]
- Nair L**, Tseng PS, Manninen PH, Teo WS. Anaesthetic management of idiopathic long QT syndrome--a case report. *Ann Acad Med Singapore* 1994; **23**: 582-585 [PMID: 7979136]

- 17 **Carlock FJ**, Brown M, Brown EM. Isoflurane anaesthesia for a patient with long Q-T syndrome. *Can Anaesth Soc J* 1984; **31**: 83-85 [PMID: 6692179 DOI: 10.1007/BF03011487]
- 18 **Brown M**, Liberthson RR, Ali HH, Lowenstein E. Perioperative anesthetic management of a patient with long Q-T syndrome (LQTS). *Anesthesiology* 1981; **55**: 586-589 [PMID: 7294417 DOI: 10.1097/0000542-198111000-00020]
- 19 **Owitz S**, Pratilas V, Pratila MG, Dimich I. Anaesthetic considerations in the prolonged Q-T interval (LQTS): a case report. *Can Anaesth Soc J* 1979; **26**: 50-54 [PMID: 761113 DOI: 10.1007/BF03039454]
- 20 **Antzelevitch C**. Role of transmural dispersion of repolarization in the genesis of drug-induced torsades de pointes. *Heart Rhythm* 2005; **2**: S9-15 [PMID: 16253930 DOI: 10.1016/j.hrthm.2004.09.011]
- 21 <http://www.azcert.org/medical-pros/drug-lists/CLQTS.cfm>
- 22 **Annala P**, Yli-Hankala A, Lindgren L. Effect of atropine on the QT interval and T-wave amplitude in healthy volunteers. *Br J Anaesth* 1993; **71**: 736-737 [PMID: 8251290 DOI: 10.1093/bja/71.5.736]
- 23 **Michaloudis DG**, Kanakoudis FS, Petrou AM, Konstantinidou AS, Pollard BJ. The effects of midazolam or propofol followed by suxamethonium on the QT interval in humans. *Eur J Anaesthesiol* 1996; **13**: 364-368 [PMID: 8842657 DOI: 10.1097/00003643-199607000-00010]
- 24 **Owczuk R**, Twardowski P, Dylczyk-Sommer A, Wujtewicz MA, Sawicka W, Drogoszewska B, Wujtewicz M. Influence of promethazine on cardiac repolarisation: a double-blind, midazolam-controlled study. *Anaesthesia* 2009; **64**: 609-614 [PMID: 19453313 DOI: 10.1111/j.1365-2044.2009.05890.x]
- 25 **Owczuk R**, Wujtewicz MA, Sawicka W, Piankowski A, Polak-Krzeminska A, Morzuch E, Wujtewicz M. The effect of intravenous lidocaine on QT changes during tracheal intubation. *Anaesthesia* 2008; **63**: 924-931 [PMID: 18547294 DOI: 10.1111/j.1365-2044.2008.05525]
- 26 **Gan TJ**, White PF, Scuderi PE, Watcha MF, Kovac A. FDA "black box" warning regarding use of droperidol for post-operative nausea and vomiting: is it justified? *Anesthesiology* 2002; **97**: 287 [PMID: 12131145 DOI: 10.1097/0000542-200207000-00059]
- 27 **Richards JR**, Schneir AB. Droperidol in the emergency department: is it safe? *J Emerg Med* 2003; **24**: 441-447 [PMID: 12745049 DOI: 10.1016/S0736-4679(03)00044-1]
- 28 **Habib AS**, Gan TJ. Pro: The Food and Drug Administration Black box warning on droperidol is not justified. *Anesth Analg* 2008; **106**: 1414-1417 [PMID: 18420854 DOI: 10.1213/ane.0b013e31816ba463]
- 29 **Kao LW**, Kirk MA, Evers SJ, Rosenfeld SH. Droperidol, QT prolongation, and sudden death: what is the evidence? *Ann Emerg Med* 2003; **41**: 546-558 [PMID: 12658255 DOI: 10.1067/mem.2003.110]
- 30 **Ludwin DB**, Shafer SL. Con: The black box warning on droperidol should not be removed (but should be clarified!). *Anesth Analg* 2008; **106**: 1418-1420 [PMID: 18420855 DOI: 10.1213/ane.0b013e3181684e6a]
- 31 **Schroeter E**, Schmitz A, Haas T, Weiss M, Gerber AC. [Low-dose droperidol in children: rescue therapy for persistent postoperative nausea and vomiting]. *Anaesthesist* 2012; **61**: 30-34 [PMID: 22234576 DOI: 10.1007/s00101-011-1962-4]
- 32 **Staikou C**, Chondrogiannis K, Mani A. Perioperative management of hereditary arrhythmogenic syndromes. *Br J Anaesth* 2012; **108**: 730-744 [PMID: 22499746 DOI: 10.1093/bja/aes105]
- 33 **Medak R**, Benumof JL. Perioperative management of the prolonged Q-T interval syndrome. *Br J Anaesth* 1983; **55**: 361-364 [PMID: 6838750 DOI: 10.1093/bja/55.4.361]
- 34 **Chang DJ**, Kweon TD, Nam SB, Lee JS, Shin CS, Park CH, Han DW. Effects of fentanyl pretreatment on the QTc interval during propofol induction. *Anaesthesia* 2008; **63**: 1056-1060 [PMID: 18616522 DOI: 10.1111/j.1365-2044.2008.05559.x]
- 35 **Wisely NA**, Shipton EA. Long QT syndrome and anaesthesia. *Eur J Anaesthesiol* 2002; **19**: 853-859 [PMID: 12510903]
- 36 **Gallagher JD**, Weindling SN, Anderson G, Fillinger MP. Effects of sevoflurane on QT interval in a patient with congenital long QT syndrome. *Anesthesiology* 1998; **89**: 1569-1573 [PMID: 9856735 DOI: 10.1097/0000542-199812000-00038]
- 37 **Song MK**, Bae EJ, Baek JS, Kwon BS, Kim GB, Noh CI, Choi JY, Park SS. QT Prolongation and Life Threatening Ventricular Tachycardia in a Patient Injected With Intravenous Meperidine (Demerol®). *Korean Circ J* 2011; **41**: 342-345 [PMID: 21779290 DOI: 10.4070/kcj.2011.41.6.342]
- 38 **Blair JR**, Pruett JK, Crumrine RS, Balser JJ. Prolongation of QT interval in association with the administration of large doses of opiates. *Anesthesiology* 1987; **67**: 442-443 [PMID: 2888423 DOI: 10.1097/0000542-198709000-00033]
- 39 **Yildirim H**, Adanir T, Atay A, Katircioglu K, Savaci S. The effects of sevoflurane, isoflurane and desflurane on QT interval of the ECG. *Eur J Anaesthesiol* 2004; **21**: 566-570 [PMID: 15318470]
- 40 **Schmeling WT**, Warltier DC, McDonald DJ, Madsen KE, Atlee JL, Kampine JP. Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. *Anesth Analg* 1991; **72**: 137-144 [PMID: 1898684 DOI: 10.1213/0000539-199102000-00001]
- 41 **Michaloudis D**, Fraidakis O, Lefaki T, Dede I, Kanakoudes F, Askitopoulou H, Pollard BJ. Anaesthesia and the QT interval in humans. The effects of isoflurane and halothane. *Anaesthesia* 1996; **51**: 219-224 [PMID: 8712319 DOI: 10.1111/j.1365-2044.1996.tb13636.x]
- 42 **Owczuk R**, Wujtewicz MA, Sawicka W, Lasek J, Wujtewicz M. The Influence of desflurane on QTc interval. *Anesth Analg* 2005; **101**: 419-22, table of contents [PMID: 16037155 DOI: 10.1213/01.ANE.0000154198.41162.FA]
- 43 **Karagöz AH**, Basgul E, Celiker V, Aypar U. The effect of inhalational anaesthetics on QTc interval. *Eur J Anaesthesiol* 2005; **22**: 171-174 [PMID: 15852988 DOI: 10.1017/S026502150500030X]
- 44 **Saussine M**, Massad I, Raczk F, Davy JM, Frapier JM. Torsade de pointes during sevoflurane anesthesia in a child with congenital long QT syndrome. *Paediatr Anaesth* 2006; **16**: 63-65 [PMID: 16409532 DOI: 10.1111/j.1460-9592.2005.01593.x]
- 45 **Paventi S**, Santevecchi A, Ranieri R. Effects of sevoflurane versus propofol on QT interval. *Minerva Anestesiol* 2001; **67**: 637-640 [PMID: 11731753]
- 46 **Nakao S**, Hatano K, Sumi C, Masuzawa M, Sakamoto S, Ikeda S, Shingu K. Sevoflurane causes greater QTc interval prolongation in elderly patients than in younger patients. *Anesth Analg* 2010; **110**: 775-779 [PMID: 20185656 DOI: 10.1213/ANE.0b013e3181cde713]
- 47 **Gürkan Y**, Canatay H, Agacdiken A, Ural E, Tokur K. Effects of halothane and sevoflurane on QT dispersion in paediatric patients. *Paediatr Anaesth* 2003; **13**: 223-227 [PMID: 12641684 DOI: 10.1046/j.1460-9592.2003.01041]
- 48 **Kleinsasser A**, Kuenszberg E, Loeckinger A, Keller C, Hermann C, Lindner KH, Puehringer F. Sevoflurane, but not propofol, significantly prolongs the Q-T interval. *Anesth Analg* 2000; **90**: 25-27 [PMID: 10624970 DOI: 10.1097/0000539-200001000-00006]
- 49 **Loeckinger A**, Kleinsasser A, Maier S, Furtner B, Keller C, Kuehbach G, Lindner KH. Sustained prolongation of the QTc interval after anesthesia with sevoflurane in infants during the first 6 months of life. *Anesthesiology* 2003; **98**: 639-642 [PMID: 12606907 DOI: 10.1097/0000542-200303000-00011]
- 50 **Scuderi PE**. Sevoflurane and QTc Prolongation: An Interesting Observation, or a Clinically Significant Finding? *Anesthesiology* 2010; **113**: 772-775 [PMID: 20808205 DOI: 10.1097/ALN.0b013e3181f2b088]
- 51 **Kies SJ**, Pabelick CM, Hurley HA, White RD, Ackerman MJ.

- Anesthesia for patients with congenital long QT syndrome. *Anesthesiology* 2005; **102**: 204-210 [PMID: 15618804 DOI: 10.1097/00000542-200501000-00029]
- 52 **Drake E**, Preston R, Douglas J. Brief review: anesthetic implications of long QT syndrome in pregnancy. *Can J Anaesth* 2007; **54**: 561-572 [PMID: 17602043 DOI: 10.1007/BF03022321]
  - 53 **Wilton NC**, Hantler CB. Congenital long QT syndrome: changes in QT interval during anesthesia with thiopental, vecuronium, fentanyl, and isoflurane. *Anesth Analg* 1987; **66**: 357-360 [PMID: 2882709 DOI: 10.1213/00000539-198704000-00015]
  - 54 **McConachie I**, Keaveny JP, Healy TE, Vohra S, Million L. Effect of anaesthesia on the QT interval. *Br J Anaesth* 1989; **63**: 558-560 [PMID: 2605073 DOI: 10.1093/bja/63.5.558]
  - 55 **Oji M**, Terao Y, Toyoda T, Kuriyama T, Miura K, Fukusaki M, Sumikawa K. Differential effects of propofol and sevoflurane on QT interval during anesthetic induction. *J Clin Monit Comput* 2012; Epub ahead of print [PMID: 23242843]
  - 56 **Irie T**, Kaneko Y, Nakajima T, Saito A, Kurabayashi M. QT interval prolongation and torsade de pointes induced by propofol and hypoalbuminemia. *Int Heart J* 2010; **51**: 365-366 [PMID: 20966611 DOI: 10.1536/ihj.51.365]
  - 57 **Higashijima U**, Terao Y, Ichinomiya T, Miura K, Fukusaki M, Sumikawa K. A comparison of the effect on QT interval between thiamylal and propofol during anaesthetic induction\*. *Anaesthesia* 2010; **65**: 679-683 [PMID: 20528837 DOI: 10.1111/j.1365-2044.2010.06341.x]
  - 58 **Hanci V**, Aydin M, Yurtlu BS, Ayoglu H, Okayay RD, Tas E, Erdogan G, Aydogan K, Turan IO. Anesthesia induction with sevoflurane and propofol: evaluation of P-wave dispersion, QT and corrected QT intervals. *Kaohsiung J Med Sci* 2010; **26**: 470-477 [PMID: 20837343 DOI: 10.1016/S1607-551X(10)70074-7]
  - 59 **Kleinsasser A**, Loeckinger A, Lindner KH, Keller C, Boehler M, Puehringer F. Reversing sevoflurane-associated Q-Tc prolongation by changing to propofol. *Anaesthesia* 2001; **56**: 248-250 [PMID: 11251432 DOI: 10.1046/j.1365-2044.2001.01717]
  - 60 **Lischke V**, Wilke HJ, Probst S, Behne M, Kessler P. Prolongation of the QT-interval during induction of anesthesia in patients with coronary artery disease. *Acta Anaesthesiol Scand* 1994; **38**: 144-148 [PMID: 8171949 DOI: 10.1111/j.1399-6576.1994.tb03856.x]
  - 61 **Erdil F**, Demirbilek S, Begec Z, Ozturk E, Ersoy MO. Effects of propofol or etomidate on QT interval during electroconvulsive therapy. *J ECT* 2009; **25**: 174-177 [PMID: 19225403 DOI: 10.1097/YCT.0b013e3181903fa5]
  - 62 **Plötz J**, Heidegger H, von Hugo R, Grohmann H, Deeg KH. [Hereditary prolonged QT interval (Romano-Ward syndrome) in a female patient with non-elective cesarean section]. *Anaesthesist* 1992; **41**: 88-92 [PMID: 1562098]
  - 63 **Strickland RA**, Stanton MS, Olsen KD. Prolonged QT syndrome: perioperative management. *Mayo Clin Proc* 1993; **68**: 1016-1020 [PMID: 8412352 DOI: 10.1016/S0025-6196(12)62277-0]
  - 64 **Finfer SR**. Pacemaker failure on induction of anaesthesia. *Br J Anaesth* 1991; **66**: 509-512 [PMID: 2025481 DOI: 10.1093/bja/66.4.509]
  - 65 **Lorentz MN**, Ramiro FG. [Anesthesia and the long QT syndrome.]. *Rev Bras Anesthesiol* 2007; **57**: 543-548 [PMID: 19462131]
  - 66 **Korpinen R**, Saarnivaara L, Siren K, Sarna S. Modification of the haemodynamic responses to induction of anaesthesia and tracheal intubation with alfentanil, esmolol and their combination. *Can J Anaesth* 1995; **42**: 298-304 [PMID: 7788827 DOI: 10.1007/BF03010706]
  - 67 **Charbit B**, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J. Prolongation of QTc interval after post-operative nausea and vomiting treatment by droperidol or ondansetron. *Anesthesiology* 2005; **102**: 1094-1100 [PMID: 15915019 DOI: 10.1097/00000542-200506000-00006]
  - 68 **Ackerman MJ**. The long QT syndrome: ion channel diseases of the heart. *Mayo Clin Proc* 1998; **73**: 250-269 [PMID: 9511785 DOI: 10.4065/73.3.250]
  - 69 **Crotti L**, Spazzolini C, Schwartz PJ, Shimizu W, Denjoy I, Schulze-Bahr E, Zaklyazminskaya EV, Swan H, Ackerman MJ, Moss AJ, Wilde AA, Horie M, Brink PA, Insolia R, De Ferrari GM, Crimi G. The common long-QT syndrome mutation KCNQ1/A341V causes unusually severe clinical manifestations in patients with different ethnic backgrounds: toward a mutation-specific risk stratification. *Circulation* 2007; **116**: 2366-2375 [PMID: 17984373 DOI: 10.1161/CIRCULATIONAHA.107.726950]
  - 70 **Garson A**. How to measure the QT interval--what is normal? *Am J Cardiol* 1993; **72**: 14B-16B [PMID: 8256749 DOI: 10.1016/0002-9149(93)90034-A]
  - 71 **Moss AJ**, Robinson J. Clinical features of the idiopathic long QT syndrome. *Circulation* 1992; **85**: I140-I144 [PMID: 1345816]
  - 72 **Levine E**, Rosero SZ, Budzikowski AS, Moss AJ, Zareba W, Daubert JP. Congenital long QT syndrome: considerations for primary care physicians. *Cleve Clin J Med* 2008; **75**: 591-600 [PMID: 18756841 DOI: 10.3949/ccjm.75.8.591]
  - 73 **Wilde AA**, Jongbloed RJ, Doevendans PA, Düren DR, Hauer RN, van Langen IM, van Tintelen JP, Smeets HJ, Meyer H, Geelen JL. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *J Am Coll Cardiol* 1999; **33**: 327-332 [PMID: 9973011 DOI: 10.1016/S0735-1097(98)00578-6]
  - 74 **Shimizu W**, Noda T, Takaki H, Nagaya N, Satomi K, Kurita T, Suyama K, Aihara N, Sunagawa K, Echigo S, Miyamoto Y, Yoshimasa Y, Nakamura K, Ohe T, Towbin JA, Priori SG, Kamakura S. Diagnostic value of epinephrine test for genotyping LQT1, LQT2, and LQT3 forms of congenital long QT syndrome. *Heart Rhythm* 2004; **1**: 276-283 [PMID: 15851169 DOI: 10.1016/j.hrthm.2004.04.021]
  - 75 **Gupta A**, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J* 2007; **153**: 891-899 [PMID: 17540188 DOI: 10.1016/j.ahj.2007.01.040]

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## Renal sympathetic denervation in resistant hypertension

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### Abstract

Resistant hypertension remains a major clinical problem despite the available multidrug therapy. Over the next decades, its incidence will likely increase given that it is strongly associated with older age and obesity. Resistant hypertension patients have an increased cardiovascular risk, thus effective antihypertensive treatment will provide substantial health benefits. The crosstalk between sympathetic nervous system and kidneys plays a crucial role in hypertension. It influences several pathophysiological mechanisms such as the central sympathetic tone, the sodium balance and the systemic neurohumoral activation. In fact, studies using several animal models demonstrated that the renal denervation prevented and attenuated hypertension in multiple species. Large reductions in blood pressure were also observed in malignant hypertension patients submitted to sympathectomy surgeries. However, these approaches had an unacceptably high rates of periprocedural complications and disabling adverse events. Recently, an innovative non-pharmacological therapy that modulates sympathetic activation has been successfully developed. Renal sympathetic percutaneous denervation is an endovascular procedure that uses radiofrequency energy to destroy the autonomic renal nerves running inside the adventitia of

renal arteries. This method represents a promising new approach to the strategy of inhibiting the sympathetic nervous system. The aim of this review is to examine the background knowledge that resulted in the development of this hypertension treatment and to critically appraise the available clinical evidence.

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**Key words:** Arterial hypertension; Sympathetic activity; Renal denervation; Percutaneous ablation; Resistant hypertension

**Core tip:** Renal percutaneous denervation allows modulating the central sympathetic tone and is a promising new approach to our old strategy of inhibiting sympathetic system. In this review we describe the pathophysiological knowledge that encouraged the development of this procedure. We critically examine the available clinical evidence of the impact of renal denervation on resistant hypertension. After describing the procedure and how to select the adequate patients, we discuss the future potential therapeutic roles in other disease conditions beyond resistant hypertension.

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### INTRODUCTION

Essential hypertension remains an important clinical challenge for both the individual as well as the public perspective<sup>[1]</sup>. Despite the several available antihypertensive drugs and their unquestionable beneficial effects, hypertension control is still unsatisfactory<sup>[2,3]</sup>. This problem can be explained by several factors, such as inappropriate blood pressure measurement, physician inertia, poor ad-

herence to therapy, excessive salt intake or the existence of secondary causes of hypertension<sup>[4]</sup>. Nevertheless, even after addressing these factors, uncontrolled hypertension persists in a significant proportion of patients. Resistant hypertension is defined as blood pressure that remains above the goal pressure despite the use of at least 3 antihypertensive drugs of different classes (one being a diuretic)<sup>[5]</sup>. The prevalence of resistant hypertension varies between 8.9% in the National Health and Nutritional Examination Survey and 50% in the ALLHAT Study<sup>[6]</sup>. Recently, in a large Spanish cohort of treated hypertensive patients, 12.2% exhibited resistant hypertension<sup>[7]</sup>. Over the next few decades, this incidence will likely increase given that it is strongly associated with older age and obesity<sup>[8]</sup>. The treatment of resistant hypertensive patients has not been directly studied<sup>[9]</sup>. However, their increased cardiovascular risk suggests that effective antihypertensive treatment will provide substantial health benefits.

Accumulated evidence indicates that human sympathetic nervous system deregulation contributes to the development of arterial hypertension<sup>[10]</sup>. Sympathetic overactivity has been demonstrated in both essential and secondary forms of hypertension patients, such as obstructive sleep apnea and obesity-related hypertension<sup>[11]</sup>. Over the last few decades, the focus of hypertension research has been the renin-angiotensin system<sup>[12]</sup>. Despite the indisputable efficacy and safety of drugs that inhibit the renin-angiotensin axis, reducing sympathetic chronic activation could be important in a significant proportion of uncontrolled hypertensive patients<sup>[13]</sup>. The aim of this review is to critically examine the relevance of renal sympathetic denervation in hypertension treatment.

## RENAL SYMPATHETIC DENERVATION: FROM THE BENCH TO THE BEDSIDE

### *Rationale for renal sympathetic denervation*

On the one hand, renal sympathetic nerve fibers critically influence renal function<sup>[14]</sup>. Adrenergic fibers innervate the most relevant renal structures such as the renal vasculature, the tubular epithelial cells throughout the nephron and the juxtaglomerular apparatus<sup>[15]</sup>. Increased renal sympathetic nerve activity results in a decrease in renal blood flow mediated by vasoconstriction ( $\alpha$ 1a adrenoceptors)<sup>[16]</sup>, increased renal tubular sodium and water reabsorption ( $\alpha$ 1b adrenoceptors)<sup>[17,18]</sup>, and an increased renin secretion rate ( $\beta$ 1 adrenoceptors)<sup>[19,20]</sup>. These effects are dependent on the degree of sympathetic activation and are considered to play an important role in the development and maintenance of hypertension<sup>[21]</sup>.

On the other hand, the kidneys can also influence the sympathetic system activity. Renal structures are richly innervated with baroreceptors and chemoreceptors<sup>[22]</sup>. These afferent nerves respond to various stimuli such as renal ischemia, hypoxia and oxidative stress<sup>[23,24]</sup>. The afferent signaling from the kidneys is transmitted to the central nervous system and enhances sympathetic outflow<sup>[25]</sup>, not only to the kidneys but also to other struc-

tures such as the heart and peripheral arterioles<sup>[26]</sup>.

It has been feasible to study the sympathetic activation in hypertensive patients by using different methods that measure sympathetic activity, such as microneurography<sup>[27,28]</sup>, noradrenaline spillover<sup>[29,30]</sup> and heart rate variability<sup>[31]</sup>. A higher sympathetic nervous activation was documented in essential hypertension, obesity-related hypertension, end-stage renal disease hypertension and in obstructive sleep apnea<sup>[29,32-34]</sup>. Interestingly, multiple studies have shown that 50% of hypertensive patients had an increased sympathetic activity in the kidneys and skeletal muscle vessels<sup>[11,28]</sup>.

In conclusion, this crosstalk between the kidneys and sympathetic nerves, and its role in hypertension pathophysiology disclosed renal nerves as an interesting potential therapeutic target.

## RENAL SYMPATHETIC DENERVATION

### *Preclinical studies*

The importance of renal sympathetic nerves in hypertension was suggested when its increased activity was described in genetically spontaneously hypertensive rats compared with normotensive controls<sup>[35]</sup>. Several animal models had been used to study the influence of renal sympathetic fibers on hypertension<sup>[36]</sup>. In an experimental model of hypertension associated with obesity, high-fat diet-fed dogs that underwent renal denervation did not exhibit a significant increase in blood pressure compared with the sham group and had a 50% reduction of sodium retention<sup>[37]</sup>. Additionally, in a chronic renal failure rat model, where the animals underwent a 5/6 nephrectomy, bilateral dorsal rhizotomy prevented blood pressure increases. The procedure also resulted in lower neuroadrenergic activity in integrative central nervous structures<sup>[38]</sup>. It was also effective in a salt-sensitive hypertension model, where renal denervation prevented blood pressure increase and normalized the sodium balance<sup>[39]</sup>. Ye *et al.*<sup>[40]</sup> elegantly demonstrated the importance of the renal sympathetic nervous system in hypertension. In this study, kidney damage was induced by intrarenal injection of phenol in rats, which caused a persistent elevation of the blood pressure and an increase in norepinephrine secretion in the hypothalamus, even in the absence of renal failure. In this model, performing renal denervation prevented the blood pressure increase.

The efficacy of renal denervation in several models and in multiple species established the key role of renal nerves in hypertension pathophysiology.

### *Clinical studies*

**Surgical sympathectomy:** Before antihypertensive drugs became available, the therapeutic option for severe or malignant hypertension was almost limited to surgical sympathectomy. Several surgical approaches with different degrees of aggressiveness were undertaken, which determined the therapeutically effectiveness and the extent of the side effects<sup>[41]</sup>. Total sympathectomy (or splanchnicectomy) surgeries were very aggressive and

were later replaced by a more conservative approaches consisting of the removal of the sympathetic ganglia from the 8<sup>th</sup> to the 12<sup>th</sup> vertebra<sup>[42]</sup>. Several studies in patients with malignant hypertension documented that sympathectomy surgeries were associated with substantial reductions in blood pressure and an increased survival rate<sup>[43]</sup>. Favorable changes in target organ damage were also confirmed<sup>[44]</sup>. However, these approaches were associated with high periprocedural complication rates and common adverse events such as orthostatic hypotension and tachycardia, intestinal disturbances, anhidrosis, and sexual dysfunction<sup>[45]</sup>. After the development of pharmacological treatment options, these surgeries were reserved only for severe hypertension patients refractory to pharmacological treatment. Surgical and renal percutaneous sympathectomies are quite different procedures concerning the extent of denervation in particular. Nevertheless, the surgical sympathectomy studies were important because they first demonstrated that the disruption of human splanchnic autonomic fibers was associated with significant reductions in blood pressure.

**Percutaneous sympathectomy:** The first clinical study that assessed the effect of percutaneous sympathetic renal denervation in hypertension patients was published in 2009. Symplicity HTN-1<sup>[46]</sup> was a safety and proof-of-principle cohort study that enrolled 45 patients (mean age  $58 \pm 9$  years) with resistant hypertension (defined as systolic blood pressure  $> 160$  mmHg despite the use of at least 3 antihypertensive drugs, including a diuretic). These patients underwent a bilateral application of radiofrequency to the renal arteries. The office blood pressures after the procedure were reduced by 14/10 mmHg at 1 mo and 27/17 mmHg at 12 mo. No favorable change in blood pressure occurred in 13% of patients. This antihypertensive effect is sustained at least up to 24 mo after the procedure<sup>[47]</sup>. Additionally, a significant reduction (42%) in renal and total body norepinephrine spillover was observed in a small subgroup of the patients who underwent sympathetic activity measurements<sup>[46]</sup>.

This cohort study was followed by a multicentre, prospective, randomized trial named Symplicity HTN-2 trial<sup>[48]</sup> published in 2010. One hundred and six patients with resistant hypertension were randomly allocated to renal denervation plus conventional antihypertensive drugs versus antihypertensive drugs only. The primary end-point was an office systolic blood pressure at the 6-mo follow-up visit. The office blood pressure in the catheter-based sympathectomy group indicated a reduction of 32/12 mmHg at the end of this period. The home and ambulatory blood pressure confirmed the observed office blood pressure changes falling by 20/12 and 11/7 mmHg, respectively, at 6 mo. No blood pressure changes occurred in the control group. At 12-mo follow-up, the magnitude of clinical response was sustained<sup>[49]</sup>. Although these trials have shown a significant blood pressure overall reduction, 13% ( $n = 6$ ) and 10% ( $n = 5$ ) of patients that underwent renal denervation had no decrease in systolic blood pressure in Symplicity HTN-1 and Symplicity

HTN-2, respectively. No predictor of nonresponse was found in univariate analysis of these patients' clinical and procedural characteristics. We can speculate that the procedure might have failed to obtain an adequate renal denervation. Another hypothetical explanation is the heterogeneous contribution of sympathetic activity to hypertension pathophysiology. The identification of the appropriate candidates to renal denervation is a challenge that should be answered by forthcoming studies. Recently, the published interventional and observational studies on renal denervation have been systematically reviewed<sup>[50]</sup>. All studies reported significant reductions in blood pressure of resistant hypertension patients.

Brandt *et al.*<sup>[51]</sup> demonstrated that renal denervation in resistant hypertension patients was associated with a regression of left ventricle hypertrophy and an improvement of the diastolic function at 6-mo follow-up visit, compared with the control group. Interestingly, a significant decrease in the left ventricular mass was also observed in patients who did not have a significant decrease in blood pressure.

## CRITICAL APPRAISAL OF TREATMENT STUDIES RESULTS

The results of the Symplicity trials are promising. Nevertheless, several limitations must be considered. Symplicity HTN-2 was an open-label trial, which means that the physician who performed the blood pressure measurement was not blinded to the type of treatment. Therefore, we cannot rule-out an ascertainment bias. In addition, there was no sham procedure in the control group, thus we cannot measure the extent of the placebo effect. The effect of treatment in the office blood pressure was concordant but more pronounced than the ambulatory blood pressure. Although this observation could represent a higher sympathetic activation with the office blood pressure measurement than during ambulatory monitoring, this discrepancy needs further elucidation. The small number of patients, the short period of follow-up and the absence of studies with hard clinical end-points precludes the establishment of the true antihypertensive effect and its prognostic importance. Some of these limitations will be addressed by the Symplicity HTN-3 trial<sup>[52]</sup>. This prospective, masked procedure, single-blind trial will randomize 530 patients and will include as a major secondary end-point, the change in the average 24-h systolic blood pressure by ambulatory blood pressure monitoring.

## SAFETY DATA

In the larger cohort of patients that underwent percutaneous renal denervation ( $n = 153$ )<sup>[47]</sup>, 97% experienced no complications. The four procedural complications included three pseudoaneurysm-hematomas in the arterial access site and one renal artery dissection that occurred before radiofrequency energy delivery in that artery. They were all managed without any long-term sequelae. The

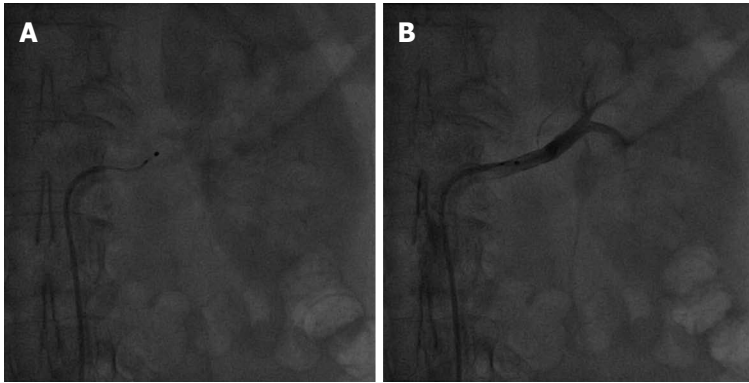


Figure 1 Left renal artery angiogram showing the catheter inside the artery.

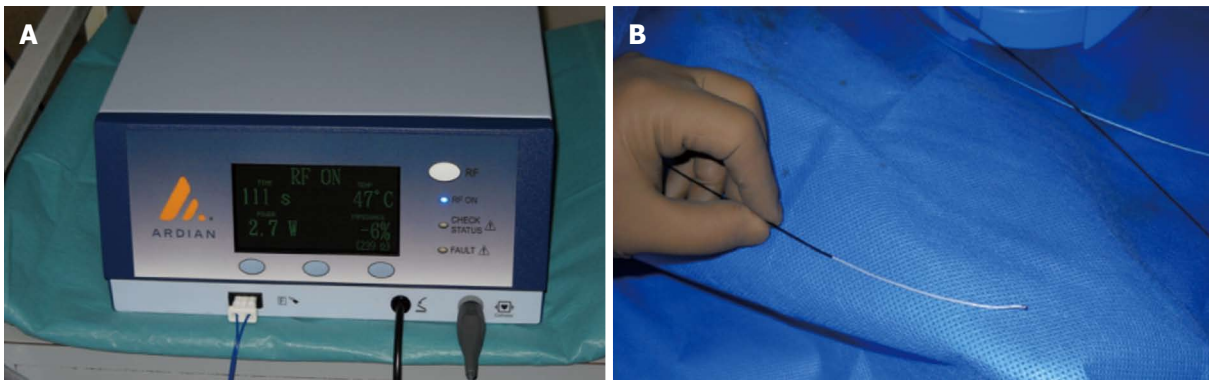


Figure 2 The Symplicity catheter and the radiofrequency console.

small number of procedures does not allow a strong conclusion to be made about the periprocedural safety of renal percutaneous denervation. Nevertheless, considering that the technique and the diameter of catheters are the same of coronary angiography, local femoral artery complications will likely have an incidence similar to coronary interventional procedures. In Symplicity HTN-2<sup>[48]</sup>, there was one pseudoaneurysm-hematoma and no other major complication. Although the intensity of the radiofrequency energy is lower than the one used for pulmonary vein isolation in atrial fibrillation ablation, renal artery stenosis is a concern. In Symplicity HTN-2, 43 of 49 patients in the intervention group underwent renal artery imaging at the 6-mo follow-up, and no significant stenosis was diagnosed. Regarding renal function, the estimated glomerular filtration rate was stable up to 24 mo of follow-up<sup>[47,53]</sup>.

The available evidence from clinical studies reveals that catheter-based renal denervation has an excellent short-term safety profile. Although unlikely, a risk of renal artery stenosis during long-term follow-up cannot be excluded.

## RENAL SYMPATHETIC DENERVATION: FROM TRIALS TO REAL LIFE

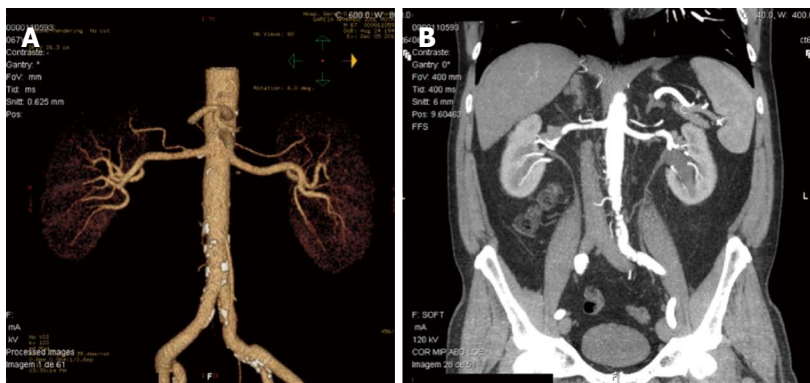
### *Description of the procedure*

The purpose of catheter-based renal sympathetic nerve ablation is to destroy the renal nerves that form a mesh-

like organization inside the adventitia. This destruction is accomplished by inserting a catheter capable of delivering radiofrequency energy into the renal artery lumen. First, a guide catheter is engaged in the renal artery ostium by femoral percutaneous access. Then, a catheter specifically designed for renal denervation<sup>[54]</sup> (Symplicity, Ardian, Palo Alto, CA, United States) is introduced into the renal artery. The tip of the catheter has an electrode that is positioned, under fluoroscopic guidance (Figure 1), in contact with the artery wall to deliver low-power (less than 8 watts) radiofrequency energy for short time intervals (up to 2 min). During ablation, the catheter system continually monitors the temperature and impedance to adjust the energy that is being delivered (Figure 2). The procedure elicits abdominal visceral pain that can be managed with analgesic and sedative drugs. The denervation requires up to six separate ablations, longitudinally and circumferentially in each renal artery. The duration of this minimally invasive procedure is approximately 45 min.

### **Starting a program of percutaneous renal denervation: our experience**

We deal with an increasing number of resistant hypertension patients during our daily clinical activity. When general measures and drug therapy optimization fail to control hypertension, we then consider another treatment option for our patients. The implementation of our percutaneous renal denervation program was governed by two main concerns: minimizing the risk of the procedure



**Figure 3** Computed tomography angiography revealing normal renal arteries of a resistant hypertension patient.

and selecting the adequate patients.

### **How to minimize the risk of the procedure?**

Despite the simplicity of this minimally invasive technique, an experienced interventional cardiologist performs the procedure. In addition to the skills needed to deal with arterial access, the certified training in this specific technique is important to assure a safe and efficient procedure. We also collaborate with an anesthesiologist, which is extremely helpful in managing the visceral pain commonly induced during the radiofrequency ablation. Our patients remain in the hospital for 24 h after the procedure for clinical monitoring. After discharge, we schedule clinical appointments at one, three, six and twelve months after the intervention.

### **How to select the patients?**

Based on the available clinical studies, adult hypertensive patients are eligible for renal denervation if they have a systolic blood pressure of 160 mmHg or more ( $> 150$  mmHg in patients with type 2 diabetes) despite treatment with three or more antihypertensive drugs, including one diuretic. Patients are not candidates for renal denervation if they have a renal artery anatomy that precludes treatment such as a diameter less than 4 mm, length less than 20 mm or the presence of more than one main renal arteries (Figure 3). Another exclusion criterion is an estimated glomerular filtration rate of less than 45 mL/min per 1.73 m<sup>2</sup>.

Before assessing whether patients meet the inclusion or exclusion criteria for the clinical studies, we evaluate the patients according to a clinical protocol<sup>[9,55]</sup>. First, we exclude those with pseudoresistance hypertension by repeating office blood pressure measurements, and we rule-out the common white-coat effect with an ambulatory blood pressure monitoring. Then, we screen for secondary causes of hypertension and, subsequently, confirm an adequate treatment regimen (up titrate to maximum tolerated doses) and patient adherence. If the blood pressure is still not controlled, we prescribe other agents as needed and tolerated such as beta-blockers, chlorthalidone or furosemide, spironolactone, and/or centrally acting sympathetic suppressants. At the end of this work-up, if the blood pressure is higher than the target goals, we assess

the patient eligibility criteria for renal denervation.

## **FUTURE PERSPECTIVES**

This new treatment explores a revolutionary principle that allows the modulation of the sympathetic central tone and can have a beneficial role in cardiovascular diseases beyond resistant hypertension<sup>[56,57]</sup>. Renal denervation has the potential of being beneficial in milder forms of hypertension<sup>[58]</sup> or secondary forms such as end-stage renal disease-related hypertension<sup>[59,60]</sup> where sympathetic overactivity has been demonstrated. Insulin sensitivity was improved in essential hypertensive<sup>[61]</sup> and obstructive sleep apnea-related hypertension patients<sup>[62]</sup>, revealing a potential role in metabolic syndrome management<sup>[63]</sup>. The maladaptive role of the chronic activation of the sympathetic nervous system is a well-known hallmark of heart failure pathophysiology<sup>[64]</sup>. Clinical studies with renal sympathetic denervation in heart failure patients are currently being performed<sup>[65,66]</sup>. We are tempted to speculate on the potential therapeutic role of renal denervation in other diseases such as hepatorenal syndrome and polycystic ovary syndrome<sup>[67]</sup>. Selective renal sympathetic denervation is a novel and promising technique that opened a new window of opportunities that deserve to be explored.

## **CONCLUSION**

Over the last few decades, growing knowledge about the role of the sympathetic chronic activation in the pathophysiology of hypertension has resulted in the development of the catheter-based renal sympathetic nerve ablation. This minimally invasive procedure pursues the efficacy of surgical sympathectomy and the safety of drug therapy. So far, clinical studies have demonstrated impressive and consistent blood-pressure reductions in resistant hypertensive patients. We acknowledge that there is still a lack of evidence from large placebo-controlled randomized clinical trials that are currently being conducted. Nevertheless, considering the available efficacy and safety data, renal percutaneous denervation should be considered for carefully selected patients with resistant hypertension.

## REFERENCES

- 1 **Kearney PM**, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**: 217-223 [PMID: 15652604]
- 2 **Persell SD**. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension* 2011; **57**: 1076-1080 [PMID: 21502568 DOI: 10.1161/HYPERTENSIONAHA.111.170308]
- 3 **De Macedo ME**, Lima MJ, Silva AO, Alcântara P, Ramalhinho V, Carmona J. Prevalence, awareness, treatment and control of hypertension in Portugal. The PAP study. *Rev Port Cardiol* 2007; **26**: 21-39 [PMID: 17427834]
- 4 **Faselis C**, Doumas M, Papademetriou V. Common secondary causes of resistant hypertension and rational for treatment. *Int J Hypertens* 2011; **2011**: 236239 [PMID: 21423678]
- 5 **Lenfant C**, Chobanian AV, Jones DW, Roccella EJ. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension* 2003; **41**: 1178-1179 [PMID: 12756222 DOI: 10.1161/01.HYP.0000075790.33892.AE]
- 6 **Cushman WC**, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, Black HR, Hamilton BP, Holland J, Nwachuku C, Papademetriou V, Probstfield J, Wright JT, Alderman MH, Weiss RJ, Piller L, Bettencourt J, Walsh SM. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)* 2002; **4**: 393-404 [PMID: 12461301 DOI: 10.1111/j.1524-6175.2002.02045.x]
- 7 **de la Sierra A**, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011; **57**: 898-902 [PMID: 21444835 DOI: 10.1161/HYPERTENSIONAHA.110.168948]
- 8 **Daugherty SL**, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, O'Connor PJ, Selby JV, Ho PM. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; **125**: 1635-1642 [PMID: 22379110 DOI: 10.1161/CIRCULATIONAHA.111.068064]
- 9 **Calhoun DA**, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* 2008; **51**: 1403-1419 [PMID: 18391085 DOI: 10.1161/HYPERTENSIONAHA.108.189141]
- 10 **Grassi G**. Sympathetic neural activity in hypertension and related diseases. *Am J Hypertens* 2010; **23**: 1052-1060 [PMID: 20651696 DOI: 10.1038/ajh.2010.154]
- 11 **Parati G**, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J* 2012; **33**: 1058-1066 [PMID: 22507981 DOI: 10.1093/eurheartj/ehs041]
- 12 **Toth PP**. Pleiotropic effects of angiotensin receptor blockers: addressing comorbidities by optimizing hypertension therapy. *J Clin Hypertens (Greenwich)* 2011; **13**: 42-51 [PMID: 21214721 DOI: 10.1111/j.1751-7176.2010.00379.x]
- 13 **Campese VM**, Ku E, Park J. Sympathetic renal innervation and resistant hypertension. *Int J Hypertens* 2011; **2011**: 814354 [PMID: 21331158]
- 14 **DiBona GF**. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 2005; **289**: R633-R641 [PMID: 16105818 DOI: 10.1152/ajpregu.00258.2005]
- 15 **Müller J**, Barajas L. Electron microscopic and histochemical evidence for a tubular innervation in the renal cortex of the monkey. *J Ultrastruct Res* 1972; **41**: 533-549 [PMID: 4629670 DOI: 10.1016/S0022-5320(72)90054-8]
- 16 **DiBona GF**, Sawin LL. Effect of renal denervation on dynamic autoregulation of renal blood flow. *Am J Physiol Renal Physiol* 2004; **286**: F1209-F1218 [PMID: 14969998 DOI: 10.1152/ajprenal.00010.2004]
- 17 **DiBona GF**. Sympathetic nervous system and the kidney in hypertension. *Curr Opin Nephrol Hypertens* 2002; **11**: 197-200 [PMID: 11856913 DOI: 10.1097/00041552-200203000-00011]
- 18 **DiBona GF**, Sawin LL. Renal nerves in renal adaptation to dietary sodium restriction. *Am J Physiol* 1983; **245**: F322-F328 [PMID: 6614170]
- 19 **Clayton SC**, Haack KK, Zucker IH. Renal denervation modulates angiotensin receptor expression in the renal cortex of rabbits with chronic heart failure. *Am J Physiol Renal Physiol* 2011; **300**: F31-F39 [PMID: 20962112 DOI: 10.1152/ajprenal.00088.2010]
- 20 **Hendel MD**, Collister JP. Renal denervation attenuates long-term hypertensive effects of Angiotensin ii in the rat. *Clin Exp Pharmacol Physiol* 2006; **33**: 1225-1230 [PMID: 17184505 DOI: 10.1111/j.1440-1681.2006.04514.x]
- 21 **Campese VM**. Neurogenic factors and hypertension in renal disease. *Kidney Int Suppl* 2000; **75**: S2-S6 [PMID: 10828754 DOI: 10.1046/j.1523-1755.2000.07511.x]
- 22 **DiBona GF**, Kopp UC. Neural control of renal function. *Physiol Rev* 1997; **77**: 75-197 [PMID: 9016301]
- 23 **Geppetti P**, Baldi E, Castellucci A, Del Bianco E, Santicioli P, Maggi CA, Lippe IT, Amann R, Skofitsch G, Theodorsson E. Calcitonin gene-related peptide in the rat kidney: occurrence, sensitivity to capsaicin, and stimulation of adenylate cyclase. *Neuroscience* 1989; **30**: 503-513 [PMID: 2787487 DOI: 10.1016/0306-4522(89)90268-6]
- 24 **Knight DS**, Cicero S, Beal JA. Calcitonin gene-related peptide-immunoreactive nerves in the rat kidney. *Am J Anat* 1991; **190**: 31-40 [PMID: 1701958 DOI: 10.1002/aja.1001900105]
- 25 **Ciriello J**, Calaresu FR. Hypothalamic projections of renal afferent nerves in the cat. *Can J Physiol Pharmacol* 1980; **58**: 574-576 [PMID: 7417886 DOI: 10.1139/y80-095]
- 26 **Hering D**, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, Esler MD, Schlaich MP. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension* 2013; **61**: 457-464 [PMID: 23172929]
- 27 **Macefield VG**, Wallin BG, Vallbo AB. The discharge behaviour of single vasoconstrictor motoneurons in human muscle nerves. *J Physiol* 1994; **481** (Pt 3): 799-809 [PMID: 7707244]
- 28 **Lambert E**, Straznicky N, Schlaich M, Esler M, Dawood T, Hotchkiss E, Lambert G. Differing pattern of sympathoexcitation in normal-weight and obesity-related hypertension. *Hypertension* 2007; **50**: 862-868 [PMID: 17909120 DOI: 10.1161/HYPERTENSIONAHA.107.094649]
- 29 **Esler M**, Jennings G, Korner P, Willett I, Dudley F, Hasking G, Anderson W, Lambert G. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension* 1988; **11**: 3-20 [PMID: 2828236 DOI: 10.1161/01.HYP.11.1.3]
- 30 **Friberg P**, Meredith I, Jennings G, Lambert G, Fazio V, Esler M. Evidence for increased renal norepinephrine overflow during sodium restriction in humans. *Hypertension* 1990; **16**: 121-130 [PMID: 2379945 DOI: 10.1161/01.HYP.16.2.121]
- 31 **Parati G**, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension* 1995; **25**: 1276-1286 [PMID: 7768574 DOI: 10.1161/01.HYP.25.6.1276]
- 32 **Converse RL**, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912-1918 [PMID: 1454086 DOI: 10.1056/NEJM199212313272704]
- 33 **Grassi G**, Colombo M, Seravalle G, Spaziani D, Mancia G.

- Dissociation between muscle and skin sympathetic nerve activity in essential hypertension, obesity, and congestive heart failure. *Hypertension* 1998; **31**: 64-67 [PMID: 9449392 DOI: 10.1161/01.HYP.31.1.64]
- 34 **Greenwood JP**, Stoker JB, Mary DA. Single-unit sympathetic discharge: quantitative assessment in human hypertensive disease. *Circulation* 1999; **100**: 1305-1310 [PMID: 10491375 DOI: 10.1161/01.CIR.100.12.1305]
  - 35 **Thorén P**. Efferent renal nerve traffic in the spontaneously hypertensive rat. *Clin Exp Hypertens A* 1987; **9** Suppl 1: 259-279 [PMID: 3677456 DOI: 10.3109/10641968709160178]
  - 36 **DiBona GF**, Esler M. Translational medicine: the antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol* 2010; **298**: R245-R253 [PMID: 19955493 DOI: 10.1152/ajpregu.00647.2009]
  - 37 **Kassab S**, Kato T, Wilkins FC, Chen R, Hall JE, Granger JP. Renal denervation attenuates the sodium retention and hypertension associated with obesity. *Hypertension* 1995; **25**: 893-897 [PMID: 7721450 DOI: 10.1161/01.HYP.25.4.893]
  - 38 **Campese VM**, Kogosov E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. *Hypertension* 1995; **25**: 878-882 [PMID: 7721447 DOI: 10.1161/01.HYP.25.4.878]
  - 39 **O'Hagan KP**, Thomas GD, Zambraski EJ. Renal denervation decreases blood pressure in DOCA-treated miniature swine with established hypertension. *Am J Hypertens* 1990; **3**: 62-64 [PMID: 2302330]
  - 40 **Ye S**, Zhong H, Yanamadala V, Campese VM. Renal injury caused by intrarenal injection of phenol increases afferent and efferent renal sympathetic nerve activity. *Am J Hypertens* 2002; **15**: 717-724 [PMID: 12160195 DOI: 10.1016/S0895-7061(02)02959-X]
  - 41 **Hafkenschiel JH**, Fitts WT. The surgical treatment of hypertension with particular reference to adrenalectomy and sympathectomy. *Trans Am Coll Cardiol* 1955; **5**: 107-112 [PMID: 13274399]
  - 42 **Doumas M**, Faselis C, Papademetriou V. Renal sympathetic denervation and systemic hypertension. *Am J Cardiol* 2010; **105**: 570-576 [PMID: 20152255 DOI: 10.1016/j.amjcard.2009.10.027]
  - 43 **Hutchison GB**, Evans JA. Should sympathectomy for arterial hypertension be abandoned? Review of surgical therapy at the Lahey Clinic: 1950-1954. *Surg Clin North Am* 1957; **37**: 871-889 [PMID: 13433294]
  - 44 **Maitland AI**. The effect of splanchnicectomy on renal function. *Lancet* 1950; **2**: 7-10 [PMID: 15437881 DOI: 10.1016/S0140-6736(50)91819-8]
  - 45 **Grimson KS**. The surgical treatment of hypertension. *Adv Intern Med* 1947; **2**: 173-194 [PMID: 20266923]
  - 46 **Krum H**, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275-1281 [PMID: 19332353 DOI: 10.1016/S0140-6736(09)60566-3]
  - 47 **Symplcity HTN-1 Investigators**. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; **57**: 911-917 [PMID: 21403086 DOI: 10.1161/HYPERTENSIONAHA.110.163014]
  - 48 **Esler MD**, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903-1909 [PMID: 21093036 DOI: 10.1016/S0140-6736(10)62039-9]
  - 49 **Esler MD**, Krum H, Schlaich M, Schmieder RE, Böhm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. *Circulation* 2012; **126**: 2976-2982 [PMID: 23248063 DOI: 10.1161/CIRCULATIONAHA.112.130880]
  - 50 **Gosain P**, Garimella PS, Hart PD, Agarwal R. Renal sympathetic denervation for treatment of resistant hypertension: a systematic review. *J Clin Hypertens (Greenwich)* 2013; **15**: 75-84 [PMID: 23282128 DOI: 10.1111/jch.12027]
  - 51 **Brandt MC**, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 2012; **59**: 901-909 [PMID: 22381425 DOI: 10.1016/j.jacc.2011.11.034]
  - 52 **Kandzari DE**, Bhatt DL, Sobotka PA, O'Neill WW, Esler M, Flack JM, Katzen BT, Leon MB, Massaro JM, Negoita M, Oparil S, Rocha-Singh K, Straley C, Townsend RR, Bakris G. Catheter-based renal denervation for resistant hypertension: rationale and design of the SYMPPLICITY HTN-3 Trial. *Clin Cardiol* 2012; **35**: 528-535 [PMID: 22573363 DOI: 10.1002/clc.22008]
  - 53 **Mahfoud F**, Cremers B, Janker J, Link B, Vonend O, Ukena C, Linz D, Schmieder R, Rump LC, Kindermann I, Sobotka PA, Krum H, Scheller B, Schlaich M, Laufs U, Böhm M. Renal hemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. *Hypertension* 2012; **60**: 419-424 [PMID: 22733462 DOI: 10.1161/HYPERTENSIONAHA.112.193870]
  - 54 **Bertog SC**, Sobotka PA, Sievert H. Renal denervation for hypertension. *JACC Cardiovasc Interv* 2012; **5**: 249-258 [PMID: 22440489 DOI: 10.1016/j.jcin.2011.12.011]
  - 55 **Schmieder RE**, Redon J. Comment on ESH position paper: renal denervation-an interventional therapy of resistant hypertension. *J Hypertens* 2012; **30**: 2443 [DOI: 10.1097/HJH.0b013e3283599beb]
  - 56 **Bhatt DL**, Bakris GL. The promise of renal denervation. *Cleve Clin J Med* 2012; **79**: 498-500 [PMID: 22751634 DOI: 10.3949/ccjm.79a.12051]
  - 57 **Linz D**, Mahfoud F, Schotten U, Ukena C, Hohl M, Neuberger HR, Wirth K, Böhm M. Renal sympathetic denervation provides ventricular rate control but does not prevent atrial electrical remodeling during atrial fibrillation. *Hypertension* 2013; **61**: 225-231 [PMID: 23150501 DOI: 10.1161/HYPERTENSIONAHA.111.00182]
  - 58 **Doumas M**, Faselis C, Papademetriou V. Renal sympathetic denervation in hypertension. *Curr Opin Nephrol Hypertens* 2011; **20**: 647-653 [PMID: 21885968 DOI: 10.1097/MNH.0b013e32834b620c]
  - 59 **Ott C**, Schmid A, Ditting T, Sobotka PA, Veelken R, Uder M, Schmieder RE. Renal denervation in a hypertensive patient with end-stage renal disease and small arteries: a direction for future research. *J Clin Hypertens (Greenwich)* 2012; **14**: 799-801 [PMID: 23126353 DOI: 10.1111/jch.12017]
  - 60 **Hering D**, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, Sobotka PA, Böhm M, Cremers B, Esler MD, Schlaich MP. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012; **23**: 1250-1257 [PMID: 22595301 DOI: 10.1681/ASN.2011111062]
  - 61 **Mahfoud F**, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011; **123**: 1940-1946 [PMID: 21518978 DOI: 10.1161/CIRCULATIONAHA.110.991869]
  - 62 **Witkowski A**, Prejbisz A, Florkczak E, Kądziela J, Śliwiński P, Bieler P, Michałowska I, Kabat M, Warchoł E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension* 2011; **58**: 559-565 [PMID: 21844482 DOI: 10.1161/HYPERTENSIONAHA.111.173799]

- 63 **Hering D**, Esler MD, Schlaich MP. Effects of renal denervation on insulin resistance. *Expert Rev Cardiovasc Ther* 2012; **10**: 1381-1386 [PMID: 23244359 DOI: 10.1586/erc.12.140]
- 64 **Davies JE**, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, Hamady M, Hughes AD, Sever PS, Sobotka PA, Francis DP. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol* 2013; **162**: 189-192 [PMID: 23031283]
- 65 **Sobotka PA**, Krum H, Böhm M, Francis DP, Schlaich MP. The role of renal denervation in the treatment of heart failure. *Curr Cardiol Rep* 2012; **14**: 285-292 [PMID: 22392370 DOI: 10.1007/s11886-012-0258-x]
- 66 **Lim GB**. Hypertension. Cardiac effects of renal denervation. *Nat Rev Cardiol* 2012; **9**: 256 [PMID: 22430831 DOI: 10.1038/nrcardio.2012.39]
- 67 **Schlaich MP**, Straznicky N, Grima M, Ika-Sari C, Dawood T, Mahfoud F, Lambert E, Chopra R, Socratous F, Hennebry S, Eikelis N, Böhm M, Krum H, Lambert G, Esler MD, Sobotka PA. Renal denervation: a potential new treatment modality for polycystic ovary syndrome? *J Hypertens* 2011; **29**: 991-996 [PMID: 21358414 DOI: 10.1097/HJH.0b013e328344db3a]

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## Papillary fibroelastoma of the aortic valve: An unusual cause of angina

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**Key words:** Papillary fibroelastoma; Angina; Aortic valve; Surgical resection; Embolic event

**Core tip:** Papillary fibroelastoma of the aortic valve is an uncommon benign tumor of the heart which can present with embolic events. In this report we present a 54-year-old female with prior history of ST segment elevation myocardial infarction who presented with exertional chest pain. She was subsequently found to have a papillary fibroelastoma of the aortic valve.

Aryal MR, Badal M, Mainali NR, Jalota L, Pradhan R. Papillary fibroelastoma of the aortic valve: An unusual cause of angina. *World J Cardiol* 2013; 5(4): 102-105 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i4/102.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i4.102>

### Abstract

Papillary fibroelastoma of the aortic valve is an uncommon benign tumor of the heart that can present with embolic events. We report a case of 54-year-old lady with exertional chest pain and prior history of ST segment elevation myocardial infarction who was subsequently found to have a fibroelastoma of the aortic valve. The absence of angiographically significant coronary artery disease and resolution of anginal symptoms post-surgery in our patient points to the possibility of fibroelastoma causing these anginal symptoms. Although uncommon, fibroelastoma are being recognized more frequently with the help of transesophageal echocardiography. Hence, in the absence of significant coronary artery disease, we emphasize the importance of consideration of papillary fibroelastoma of the aortic valve as a cause of angina. We also discuss the key aspects of the fibroelastoma including presentation, diagnostic modalities and treatment options.

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### INTRODUCTION

Papillary fibroelastoma (PFE) is the third most common benign primary tumor of the heart that usually involves the cardiac valves. Clinical presentation of PFE varies widely, ranging from asymptomatic to severe ischemic or embolic events. PFE are being recognized more frequently with the help of transesophageal echocardiography (TEE) and should be differentiated from thrombus, vegetation, myxoma and Lambl's excrescence. Symptomatic cardiac PFE should be surgically removed whereas asymptomatic lesions that are left-sided, mobile or larger than 1 cm should be considered for surgical excision. Recurrence after surgery has not been reported, and the long-term postoperative prognosis is excellent.

Here in this report, we present a case of 54-year-old female patient with prior history of ST segment elevation myocardial infarction (STEMI) who presented with exertional chest pain. She was subsequently found to have a PFE of the aortic valve.

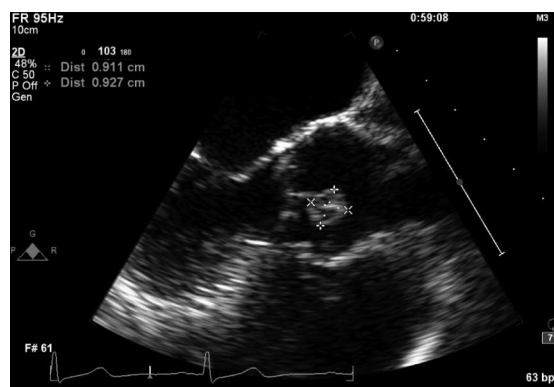
## CASE REPORT

A 54-year-old female with history of obesity, hyperlipidemia and hypertension and prior STEMI presented with exertional chest tightness of 3 mo duration. Two years prior to this presentation, she had suffered an anterior STEMI. Emergent cardiac catheterization at that time had revealed a total occlusion of distal left anterior descending (LAD) artery with no angiographic evidence of coronary atherosclerosis elsewhere. She was treated with primary balloon angioplasty and stenting was not done secondary to a small vessel caliber. She had a TTE done afterwards, which showed apical akinesis and an ejection fraction of 45%. Rest of the TTE was within normal limits including valvular anatomy and function. She was discharged on aspirin, simvastatin and metoprolol. She remained symptom free till 3 mo before presentation. She had started noticing chest tightness after joining exercise classes to lose weight. The tightness was similar in quality to her STEMI pain but much less intense in severity and resolved in 5 min after rest. Rest of her review of systems was negative.

Physical examination was unremarkable, except for obesity. Electrocardiogram did not reveal any pathological Q waves or evidence of ischemia or infarction. A treadmill stress test with myocardial perfusion imaging revealed a predominantly fixed defect at the lateral cardiac apex suggestive of the prior infarct; no ischemia was noted. A TTE done to assess left ventricular function revealed normal left ventricular function with mild hypokinesis in the prior infarct territory. However, TTE incidentally revealed a well-circumscribed 1 cm mass on the aortic side of the right coronary cusp of the aortic valve, concerning for a PFE. She had no risk factors, symptoms or signs suggestive of infective endocarditis or valvular thrombus. Further review of systems at this point failed to reveal any systemic embolic phenomenon. TEE was done to further characterize the mass. TEE revealed a well-circumscribed echo dense mass adherent to the edge of the right coronary cusp with a thin stalk and with minimal independent motion (Figure 1). The mass measured 0.9 cm in diameter. The aortic leaflets appeared normal in thickness and flexibility.

With her history of prior STEMI in the LAD territory without coronary atherosclerosis elsewhere, a concern was raised for a possible “embolic MI” in the past. As PFEs are known to cause embolic complications, especially when they are large, stalked and mobile, a recommendation was made for surgical resection of the mass. She underwent cardiac computed tomography (CT) angiography in preparation for the valve surgery to rule out obstructive coronary artery disease (instead of cardiac catheterization to prevent mass embolization with catheter manipulation). CT angiography failed to reveal any coronary atherosclerosis and reconfirmed the presence of PFE (Figure 2). Surgical removal of the mass without valve replacement was performed without complications.

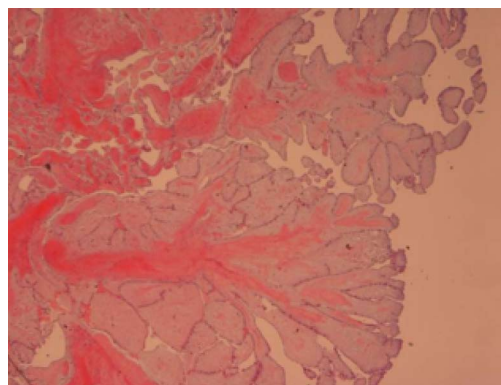
The mass measured 1.0 cm × 0.8 cm × 0.5 cm and



**Figure 1** Mid esophageal aortic valve long axis view showing the papillary fibroelastoma attached to the aortic side of the right coronary cusp.



**Figure 2** Cardiac computed tomography five chamber view showing the papillary fibroelastoma attached to the right coronary cusp.



**Figure 3** Histopathology. Hematoxylin and eosin stain showing papillary fibroelastoma with narrow, elongated and branching papillary fronds with central avascular collagen and elastic tissue (Low power view, 40 × magnification).

histopathological examination was consistent with benign papillary fibroelastoma (Figure 3). Patient remained free of symptoms after surgery.

## DISCUSSION

The prevalence of primary cardiac tumor ranges from 0.002%-0.28%<sup>[1]</sup>. Papillary fibroelastoma originates most commonly from the valvular endocardium (85%). Aortic

valve is most often involved (29%), followed by mitral valve (25%), tricuspid valve (17%) and pulmonary valves (13%)<sup>[2]</sup>. Although highest prevalence is seen in the eighth decade of life, it has been described in patients aged 6 d to 92 years<sup>[2]</sup>. Embolization is the most common clinical presentation, which may include but are not limited to stroke, myocardial infarction, mesenteric ischemia, renal infarction, limb ischemia, pulmonary embolism, and pulmonary hypertension. Patients can also present with heart failure, ventricular fibrillation and sudden death. Fibroelastoma arising from the aortic valve have been implicated in occurrence of sudden death by causing transient or complete obstruction of the ostium of coronary arteries<sup>[1,2]</sup>. Atrioventricular valve fibroelastoma can obstruct ventricular filling resulting in recurrent pulmonary edema and right-heart failure, mimicking a clinical picture of mitral or tricuspid valve stenosis. Conduction system disturbances and complete atrioventricular block have also been reported<sup>[3]</sup>. Rarely, aortic valve PFE is also noted to cause angina secondary to transient obstruction of the coronary ostium<sup>[2]</sup>.

The common differential diagnosis of PFE includes other cardiac tumors (myxoma), vegetation, thrombus and Lambl's excrescence. These can be differentiated by clinical presentation, location and character of the mass on TTE, TEE, cardiac CT or magnetic resonance imaging (MRI). The diagnosis is usually made by TTE or TEE, although, TEE is more sensitive. Echocardiography shows a small, pedunculated or sessile valvular or endocardial mobile mass, with a pedicle attached to the valve or endocardial surface and a frond-like appearance with or without multifocal involvement into the cardiac chambers. Echocardiographically, papillary fibroelastomas appear speckled with echolucencies near the edges. They have stippled edges. Mobility of the tumor is an independent predictor of nonfatal embolization and death. Computed tomography is inferior to transesophageal echocardiography in demonstrating the small moving structures. However, MRI is more valuable than computed tomography by imaging in multiple planes and better soft-tissue characterization of tumor. Gadolinium may enhance the differences between tumor and surrounding normal cardiac structures. 3-D echocardiography has also been used for better delineation of cardiac tumors<sup>[4]</sup>. Cardiac catheterization prior to resection of a PFE is subject to debate because of the friable nature of the lesion and because of the potential risk of embolization. On coronary angiography, the total occlusions or narrowing of distal coronary branches due to tumor emboli can be seen<sup>[5]</sup>.

Grossly, PFE looks like a sea anemone because of its multiple papillary fronds. Papillary fibroelastoma are small avascular tumors with a single layer of endocardial cells covering the papillary surface<sup>[5]</sup>. Matrix consists of elastic fibers, proteoglycans, and spindle cells that resemble smooth muscle cells or fibroblasts. The layer of elastic fibers is a hallmark of this tumor. The connective tissue of fibroelastoma contains longitudinally oriented collagen with irregular elastic fibers<sup>[6]</sup>.

Asymptomatic patients can be treated surgically if the tumor is mobile. Patients with asymptomatic non-mobile papillary fibroelastoma can be followed-up closely with periodic clinical evaluation and echocardiography, and they receive surgical intervention when the tumor becomes mobile or symptomatic<sup>[7]</sup>. Shave excision is successful in 83% of patients without the need for valvular repair or replacement<sup>[8]</sup>. TEE can also guide the surgical resection and assess the adequacy of valve repair both perioperatively and postoperatively. The surgical resection is curative, safe and well tolerated. Mechanical damage to the heart valve or adhesion of tumor to valve may necessitate valve repair or replacement<sup>[9]</sup>. Sastre-Garriga *et al*<sup>[10]</sup> recommend long-term anticoagulation for symptomatic patients who are not surgical candidates.

In our case, occurrence of STEMI in distal LAD with normal coronary artery elsewhere does raise a question of possible embolic myocardial infarction. The mass could have been small, or partially embolized and hence missed by the TTE at that time. PFE grows at a rate of 2-70 mm over a 1-year period<sup>[7]</sup>. The absence of angiographically significant coronary artery disease and resolution of anginal symptoms post-surgery in our patient points to the possibility of PFE causing these anginal symptoms. It is possible that the proximity of the stalked PFE on the right coronary cusp to the ostium of the right coronary artery (RCA) caused dynamic obstruction to the flow in the RCA, especially during exercise (demand ischemia); although, we could not explain the lack of ischemic findings during exercise myocardial perfusion imaging. Also, coronary vasospasm and multiple embolic events seem to be unlikely in our case as the symptoms occurred only during exertion, there was lack of electrocardiographic abnormalities and new perfusion defects during the exercise myocardial perfusion imaging. In summary, we presented a case of papillary fibroelastoma of the aortic valve causing anginal symptoms and possibly a myocardial infarction in the past.

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## REFERENCES

- 1 **Jha NK**, Khouri M, Murphy DM, Salustri A, Khan JA, Saleh MA, Von Canal F, Augustin N. Papillary fibroelastoma of the aortic valve--a case report and literature review. *J Cardiothorac Surg* 2010; 5: 84 [PMID: 20950491 DOI: 10.1186/1749-8090-5-84]
- 2 **Bruno VD**, Mariscalco G, De Vita S, Piffaretti G, Nassiaco D, Sala A. Aortic valve papillary fibroelastoma: a rare cause of angina. *Tex Heart Inst J* 2011; 38: 456-457 [PMID: 21841886]
- 3 **Thomas MR**, Jayakrishnan AG, Desai J, Monaghan MJ, Jewitt DE. Transesophageal echocardiography in the detection and surgical management of a papillary fibroelastoma of the mitral valve causing partial mitral valve obstruction. *J Am Soc Echocardiogr* 1993; 6: 83-86 [PMID: 8439427]
- 4 **Araoz PA**, Eklund HE, Welch TJ, Breen JF. CT and MR imag-

- ing of primary cardiac malignancies. *Radiographics* 1999; **19**: 1421-1434 [PMID: 10555666]
- 5 **Kumbala D**, Sharp T, Kamalesh M. "Perilous pearl"--papillary fibroelastoma of aortic valve: a case report and literature review. *Angiology* 2008; **59**: 625-628 [PMID: 18388078]
- 6 **Fishbein MC**, Ferrans VJ, Roberts WC. Endocardial papillary elastofibromas. Histologic, histochemical, and electron microscopical findings. *Arch Pathol* 1975; **99**: 335-341 [PMID: 1088858]
- 7 **Gowda RM**, Khan IA, Nair CK, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac papillary fibroelastoma: a comprehensive analysis of 725 cases. *Am Heart J* 2003; **146**: 404-410 [PMID: 12947356 DOI: 10.1016/S0002-8703(03)00249-7]
- 8 **Ngaage DL**, Mullany CJ, Daly RC, Dearani JA, Edwards WD, Tazelaar HD, McGregor CG, Orszulak TA, Puga FJ, Schaff HV, Sundt TM, Zehr KJ. Surgical treatment of cardiac papillary fibroelastoma: a single center experience with eighty-eight patients. *Ann Thorac Surg* 2005; **80**: 1712-1718 [PMID: 16242444 DOI: 10.1016/j.athoracsur.2005.04.030]
- 9 **Loire R**, Pinède L, Donsbeck AV, Nighoghossian N, Perinetti M. [Papillary fibroelastoma of the heart (giant Lambl excrescence). Clinical-anatomical study on 10 surgically treated patients]. *Presse Med* 1998; **27**: 753-757 [PMID: 9767897]
- 10 **Sastre-Garriga J**, Molina C, Montaner J, Mauleón A, Pujadas F, Codina A, Alvarez-Sabín J. Mitral papillary fibroelastoma as a cause of cardiogenic embolic stroke: report of two cases and review of the literature. *Eur J Neurol* 2000; **7**: 449-453 [PMID: 10971607]

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## Concept of defibrillation vector in the management of high defibrillation threshold

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### Abstract

We present a case where defibrillation threshold was dangerously elevated to the point that the patient had no safety margin, and his implantable cardioverter-defibrillator generator was discovered to have migrated. Generator migration reduces the distance between the can and the coil, effectively creating a smaller bipolar current and sparing the left ventricle from the current needed for defibrillation. This case underscores the importance of securing the generator in place, as this patient would have been spared multiple shocks and an invasive medical procedure had his generator been better secured.

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**Key words:** Ventricular tachycardia; Defibrillation thresh-

old; Implantable cardioverter-defibrillator; Pacemaker

**Core tip:** Defibrillation threshold can be altered by a myriad of factors including generator migration. We report a case to illustrate the concept of implantable cardioverter-defibrillator defibrillation vectors and its effect on defibrillation threshold.

Hayes K, Deshmukh A, Pant S, Tobler G, Paydak H. Concept of defibrillation vector in the management of high defibrillation threshold. *World J Cardiol* 2013; 5(4): 106-108 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i4/106.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i4.106>

### INTRODUCTION

Defibrillation threshold (DFT) is routinely performed at the time of implantable cardioverter-defibrillator (ICD) implantation, but can be altered by a myriad of factors: lead placement, medications, sympathetic tone, electrolyte alterations, and shock vectors<sup>[1,2]</sup>. “High DFT” is defined as an absolute shock value of > 25 J or a safety margin of < 10 J below the maximum device output. Elevated DFTs put the patient at heightened risk for sudden cardiac death due to inadequate defibrillation. Reports from the literature demonstrate the incidence of high DFTs between 2% and 24%<sup>[3]</sup>; however, two large studies agree on a rate of 6.2%<sup>[4,5]</sup>. Recommended approaches to the patient with high DFTs vary in the medical literature. Following options are recommended: reverse the shock polarity, change the shock configuration (e.g., tip-to-generator, ring-to-generator, tip-to-coil), modify the waveform, exchange the generator to a high-output device, discontinue medications that increase DFT if possible, add a superior vena cava coil, add a subcutaneous array, or move the generator to the left pectoral region if it is located on the right<sup>[6]</sup>. Some ICD brands allow

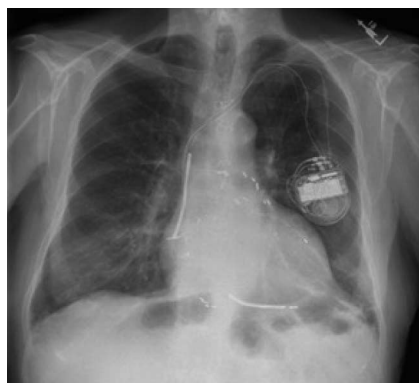
reprogramming of the shock configuration even within a single treatment window, which theoretically increases the chance of successful defibrillation. Data suggests that a configuration where the right ventricular (RV) lead is the anode results in the highest success of defibrillation, but a small population of patients benefits from the reverse configuration<sup>[3]</sup>.

## CASE REPORT

Eighty years old Caucasian male presented to device clinic for management of sustained monomorphic ventricular tachycardia (VT) leading to multiple ICD shocks. Medical history included coronary artery disease status post 3 vessel coronary artery bypass grafting in the remote past and severe ischemic cardiomyopathy with ejection fraction of 10%. Attempts were made to ablate his VT, but he continued to have episodes of appropriate ICD therapies. He had a bi-ventricular ICD (Bi-V ICD) with a lower rate of 80 beats per minute. Patient has had multiple hospitalizations in the past for appropriate ICD therapies.

Medical management of VT of the patient was complicated. He was previously managed on amiodarone, but this was stopped when his DFT became prohibitively high and obliterated the 10-joule safety margin. He was then managed with maximum dose of long acting metoprolol and did well until he started having appropriate shocks for recurrent VT. He was finally started on mexiletine, which he tolerated. One week after initiation of mexiletine he underwent repeat DFT testing. Multiple configurations and device outputs were tried unsuccessfully: 25 and 35 J from can and coil to tip; 25 and 35 J from tip to can and coil; 25 J from can to tip and tip to can. The patient was finally successfully defibrillated with 35 J from can to tip, again demonstrating a loss of safety margin.

His most recent cardiovascular work-up, including left heart catheterization, echocardiogram, and electrocardiogram showed stable, severe coronary artery disease and systolic dysfunction. A recent chest X-ray (Figure 1) shows his device in the left chest with a right atrial lead, a RV ICD lead, and a left ventricular pacing lead in the coronary sinus. He reported New York Heart Association class II symptoms, but was in good spirits. After careful review of the case, decision was made to place a right sided endocardial lead to the RV true apex which would then be tunneled to the left side. Attempts to place a pace-sensing lead from the left side at the time of ICD generator change had failed due to too many leads on the left side. If repositioning of the RV lead fails, placement of a subcutaneous array was planned. In the operating room, the device pocket was opened and it was noted that the generator had migrated substantially inferiorly across the chest wall. At this time, the generator was moved up to the subclavicular position and DFTs were retested. He was successfully defibrillated with 25 J, twice. A post-operative chest X-ray shows higher positioning of



**Figure 1** Chest X-ray demonstrating bi-ventricular implantable cardioverter defibrillator.



**Figure 2** Note the changed position of the implantable cardioverter defibrillator Generator.

the ICD can in the subclavian position (Figure 2). He was discharged home the next day safely.

## DISCUSSION

This case elegantly illustrates the concept of ICD defibrillation vectors. When the patient arrived, his DFTs were dangerously elevated to the point that he had no safety margin, and his ICD generator was discovered to have migrated. At the time of his procedure, the generator was nearly lateral to the left heart border. This malpositioning altered the electric field in that it allowed current to move anteriorly from the coil to the can, reducing the involvement of the posteriorly positioned left ventricle. Additionally, it reduced the distance between the can and the coil, effectively creating a smaller bipolar current and sparing the left ventricle from the current needed for defibrillation. This case underscores the importance of securing the generator in place, as this patient would have been spared multiple shocks and an invasive medical procedure had his generator been better secured. Even the newer, entirely subcutaneous ICD systems are reliant on proper positioning. In a recent article describing the initial Dutch experience with the device, three patients received inappropriate shocks due to lead migration. This complication was solved by adding an additional suture

sleeve<sup>[7]</sup>.

It is suggested that the RV lead be positioned to the true ventricular apex<sup>[1]</sup>. More proximal positioning of the lead results in higher DFTs, but if the RV lead is positioned closer to the interventricular septum or RV out-flow tract, DFTs are improved<sup>[3]</sup>. A recent study reported similar rates of high DFTs in patients with RV apical leads (3/108) *vs* RV septal leads (3/107)<sup>[8]</sup>. The Septal Positioning of Ventricular ICD electrodes trial is currently underway and should help to answer the question of optimal RV lead position. It is important to consider that as ICD systems adopt the dual coil single lead configuration it will become more difficult to manipulate positioning to optimize DFTs.

With repositioning of his ICD generator, we were able to restore his DFTs to a safe level by correcting the malpositioning and optimizing the shock vector. To our knowledge, this is the only such case reported in the medical literature.

## REFERENCES

- 1 **Mainigi SK**, Callans DJ. How to manage the patient with a high defibrillation threshold. *Heart Rhythm* 2006; **3**: 492-495 [PMID: 16567304 DOI: 10.1016/j.hrthm.2005.12.023]
- 2 **Bonny A**, De Sisti A, Márquez MF, Megbemedo R, Hidden-Lucet F, Fontaine G. Low doses of intravenous epinephrine for refractory sustained monomorphic ventricular tachycardia. *World J Cardiol* 2012; **4**: 296-301 [PMID: 23110246 DOI: 10.4330/wjc.v4.i10.296]
- 3 **Jacob S**, Pidlaoan V, Singh J, Bharadwaj A, Patel MB, Carrillo A. High defibrillation threshold: the science, signs and solutions. *Indian Pacing Electrophysiol J* 2010; **10**: 21-39 [PMID: 20084193]
- 4 **Russo AM**, Sauer W, Gerstenfeld EP, Hsia HH, Lin D, Cooper JM, Dixit S, Verdino RJ, Nayak HM, Callans DJ, Patel V, Marchlinski FE. Defibrillation threshold testing: is it really necessary at the time of implantable cardioverter-defibrillator insertion? *Heart Rhythm* 2005; **2**: 456-461 [PMID: 15840466 DOI: 10.1016/j.hrthm.2005.01.015]
- 5 **Osswald BR**, De Simone R, Most S, Tochtermann U, Tanzeem A, Karck M. High defibrillation threshold in patients with implantable defibrillator: how effective is the subcutaneous finger lead? *Eur J Cardiothorac Surg* 2009; **35**: 489-492 [PMID: 19144533 DOI: 10.1016/j.ejcts.2008.10.021]
- 6 **Hayes DL**, Friedman PA. Cardiac pacing, defibrillation and resynchronization: a clinical approach. 2nd ed. Oxford: Wiley-Blackwell, 2008: 25-27 [DOI: 10.1002/9781444300659]
- 7 **Olde Nordkamp LR**, Dabiri Abkenari L, Boersma LV, Maass AH, de Groot JR, van Oostrom AJ, Theuns DA, Jordaens LJ, Wilde AA, Knops RE. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. *J Am Coll Cardiol* 2012; **60**: 1933-1939 [PMID: 23062537 DOI: 10.1016/j.jacc.2012.06.053]
- 8 **Mabo P**, Defaye P, Mouton E, Cebron JP, Davy JM, Tassin A, Babuty D, Mondoly P, Paziaud O, Anselme F, Daubert JC. A randomized study of defibrillator lead implantations in the right ventricular mid-septum versus the apex: the SEPTAL study. *J Cardiovasc Electrophysiol* 2012; **23**: 853-860 [PMID: 22452288 DOI: 10.1111/j.1540-8167.2012.02311.x]

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**L- Editor** A **E- Editor** Zhang DN



## Transvenous defibrillator implantation in a patient with persistent left superior vena cava

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Author contributions: All the authors were actively involved in management of the index case.

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### Abstract

Persistent left superior vena cava (LSVC) can be incidentally detected during pacemaker implantation through left pectoral side. There is technical difficulty of optimal site pacing and lead stability for right ventricle lead in such situation. We hereby report a case of successful single-chamber implantable cardioverter defibrillator (ICD) implantation in a 50 years-old male with LSVC. The practical issues related with right ventricle lead implantation and pacing/defibrillation parameters for ICD device are discussed.

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**Key words:** Cardioverter defibrillator; Left superior vena cava; Myocardial infarction; Ventricular tachycardia

**Core tip:** Persistent left superior vena cava (LSVC) can be incidentally detected during pacemaker implantation through left pectoral side. we hereby report a case of persistent LSVC, who had successful single chamber implantable cardioverter defibrillator (ICD) implantation with dual coil active fixation lead. We achieved good functional parameters of the ICD and

had uneventful 6 mo of follow-up.

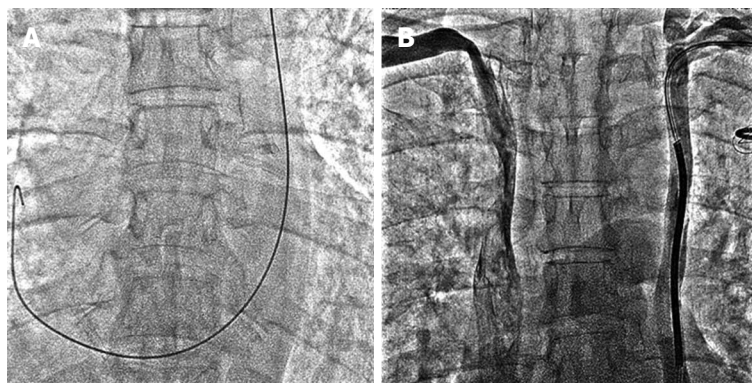
Vijayvergiya R, Shrivastava S, Kumar A, Otaal PS. Transvenous defibrillator implantation in a patient with persistent left superior vena cava. *World J Cardiol* 2013; 5(4): 109-111 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i4/109.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i4.109>

### INTRODUCTION

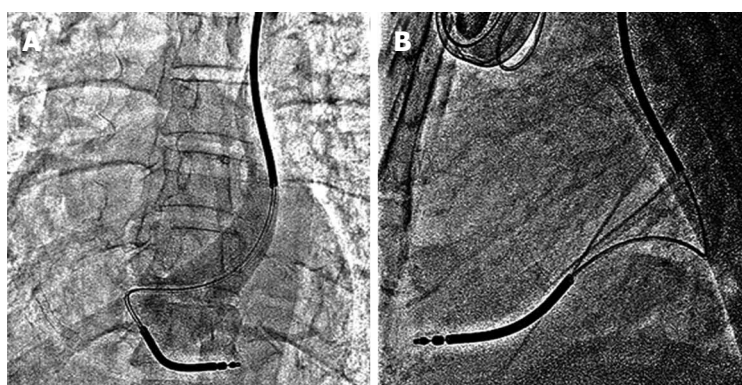
The presence of persistent left superior vena cava (LSVC) can be incidentally detected during pacemaker implantation from left pectoral side. There is technical difficulty for optimal site pacing and lead stability of right ventricle (RV) lead in such a situation. There is also a concern about optimal vector for defibrillation potential following implantable cardioverter defibrillator (ICD) implantation. We hereby report a case of single chamber ICD implantation in a 50 years-old male, who had persistent LSVC. The issues related to RV lead implantation and defibrillation threshold is discussed.

### CASE REPORT

A 50-years-old hypertensive, chronic smoker male had anterior wall myocardial infarction in November 2007, for which he underwent coronary stenting of proximal left anterior descending and proximal left circumflex arteries. Later in January 2012, he had inferior wall myocardial infarction, for which he underwent coronary stenting of mid right coronary artery. One month later, he presented with hemodynamically unstable monomorphic ventricular tachycardia of rate 200 beats/min, which was reverted by electrical cardioversion. His left ventricle (LV) ejection fraction was 0.30. A repeat coronary angiography revealed patent stents in all three coronary arteries. He was taken up for ICD implantation for secondary prevention of



**Figure 1** X-ray in Antero-posterior view shows. A: Guide wire course from left subclavian vein to right atrium across the left heart border, suggesting left superior vena cava draining into right atrium; B: Simultaneous venogram shows individual drainage of both right and left superior vena cava (SVC) to right atrium, without any bridging communicating vein between the two. Left SVC shows lead *in-situ*.



**Figure 2** X-ray in Antero-posterior (A) and lateral (B) view shows dual coil right ventricle lead implanted at right ventricle apex. Venogram in figure (A) confirms persistence of left superior vena cava.

sudden cardiac death. After conventional left subclavian vein puncture, the guide wire took the unusual course by descending across the left heart border to reach the right atrium, suggesting a persistent LSVC (Figure 1A). A contrast injection from left ante-cubital vein confirmed the presence of LSVC. There was no communicating vein between left and right superior vena cava (Figure 1B). An active fixation, dual coil RV lead (Medtronic Sprint Quattro Secure, Model No.6947, length 65 cm, 8.2 F) was passed through the LSVC-coronary sinus for implantation. A U shaped stylet was used to direct the lead from right atrium to RV. A wide loop of the lead was made in right atrium and the tip of the lead was directed towards tricuspid valve with the help of curved stylet. After few manipulations, the lead could be positioned at RV apex (Figure 2). The lead parameters were satisfactory-pacing threshold was 1.2 V at 0.5 milli-seconds pulse width, with a pacing impedance of 1098  $\Omega$ , R wave amplitude was 7.8 milli-Volts with slew rate of  $> 2.0$  Volts/s. The RV and SVC defibrillation impedance was 41 and 46 ohms, respectively. The device (Medtronic Maximo II VR, Model D284VRC) was connected with the lead and implanted in left pectoral region. The total fluoroscopy time for the procedure was 12 min. An initial 15 J shock could revert the ventricular fibrillation to normal sinus rhythm during defibrillation testing (DFT), with SVC coil in on-mode. During 6 mo of follow-up, he did not have any shock or anti-tachycardia pacing for ventricular tachycardia.

## DISCUSSION

The persistent LSVC is a remnant of embryologic venous

system<sup>[1]</sup>. Its prevalence is 0.3%-0.5% in normal population<sup>[2,3]</sup>. There is considerable anatomic variation in venous drainage with persistent LSVC. A right side superior vena cava (SVC) may be absent, or both right and left SVC if present may or may not be connected with a bridging innominate vein<sup>[3-5]</sup>. It is technically challenging to direct the pacing lead at appropriate RV site in the presence of LSVC<sup>[3,6]</sup>, as forward movement of the lead in right atrium is commonly towards SVC or IVC side and remain away from the tricuspid valve. As reported by others, we also made a manual U turn in the stylet to direct the active fixation lead from right atrium to right ventricle. After few manipulations, we could successfully screw the active fixation lead at RV apex and achieved satisfactory pacing parameters. The fluoroscopy time of 12 min was also comparable with others<sup>[4]</sup>. We have used active fixation RV lead to have adequate lead stability, as being used by other operators<sup>[3-6]</sup>. There is also a concern about optimum vector for defibrillation potential in these patients, as SVC coil is in coronary sinus and on the left side, instead of its usual right SVC position<sup>[4,7]</sup>. Few operators have used additional subcutaneous patch<sup>[8,9]</sup> or defibrillation coil<sup>[10]</sup> for the optimal defibrillation potential. Even, Tauras *et al*<sup>[11]</sup> had performed innominate vein angioplasty to put defibrillation lead via right SVC in a patient with LSVC. As there was absent bridging innominate vein in the index case (Figure 1B), we could not approach to right SVC from left side. Various authors have used a single coil lead in such a situation to avoid high defibrillation threshold<sup>[4,7]</sup>, however we achieved effective 15 J defibrillation threshold (DFT) even with dual coil lead. A newer generation device like the one we implanted (Medtronic Maximo II,

Model No. D284VRC), have an option to turn-off the SVC coil, thus make it functional as a single coil lead. This option can be tried in the index case, if tachycardia therapy is not effective at follow-up.

In conclusion, we hereby report a case of persistent LSVC, who had successful single chamber ICD implantation with dual coil active fixation lead. We achieved good functional parameters of the ICD and had uneventful 6 mo of follow-up.

## REFERENCES

- 1 **Nsah EN**, Moore GW, Hutchins GM. Pathogenesis of persistent left superior vena cava with a coronary sinus connection. *Pediatr Pathol* 1991; **11**: 261-269 [PMID: 2052508 DOI: 10.3109/15513819109064763]
- 2 **Albert M**, Geissler W. [Persistent left superior vena cava and mitral stenosis]. *Z Gesamte Inn Med* 1956; **11**: 865-874 [PMID: 13401892]
- 3 **Biffi M**, Boriani G, Frabetti L, Bronzetti G, Branzi A. Left superior vena cava persistence in patients undergoing pacemaker or cardioverter-defibrillator implantation: a 10-year experience. *Chest* 2001; **120**: 139-144 [PMID: 11451829 DOI: 10.1378/chest.120.1.139]
- 4 **Biffi M**, Bertini M, Ziacchi M, Martignani C, Valzania C, Diemberger I, Branzi A, Boriani G. Clinical implications of left superior vena cava persistence in candidates for pacemaker or cardioverter-defibrillator implantation. *Heart Vessels* 2009; **24**: 142-146 [PMID: 19337799 DOI: 10.1007/s00380-008-1091-4]
- 5 **Gasparini M**, Mantica M, Galimberti P, Coltorti F, Simonini S, Ceriotti C, Gronda E. Biventricular pacing via a persistent left superior vena cava: report of four cases. *Pacing Clin Electrophysiol* 2003; **26**: 192-196 [PMID: 12687811 DOI: 10.1046/j.1460-9592.2003.00015.x]
- 6 **Paulussen GM**, van Gelder BM. Implantation of a biven-tricular pacing system in a patient with a persistent left superior vena cava. *Pacing Clin Electrophysiol* 2004; **27**: 1014-1016 [PMID: 15271028 DOI: 10.1111/j.1540-8159.2004.00577.x]
- 7 **Arora V**, Singh J, Kler TS. Implantable cardioverter defibril-latory implantation in a patient with persistent left superior vena cava and right superior vena cava atresia. *Indian Heart J* 2005; **57**: 717-719 [PMID: 16521645]
- 8 **Mattke S**, Markewitz A, Dorwarth U, Hoffmann E, Steinbeck G. Defibrillator implantation in a patient with a persistent left superior vena cava. *Pacing Clin Electrophysiol* 1995; **18**: 117-120 [PMID: 7700825 DOI: 10.1111/j.1540-8159.1995.tb02486.x]
- 9 **Favale S**, Bardy GH, Pitzalis MV, Dicandia CD, Traversa M, Rizzon P. Transvenous defibrillator implantation in patients with persistent left superior vena cava and right superior vena cava atresia. *Eur Heart J* 1995; **16**: 704-707 [PMID: 7588905]
- 10 **Leng CT**, Crosson JE, Calkins H, Berger RD. Lead configura-tion for defibrillator implantation in a patient with congenital heart disease and a mechanical prosthetic tricuspid valve. *Pacing Clin Electrophysiol* 2001; **24**: 1291-1292 [PMID: 11523619 DOI: 10.1046/j.1460-9592.2001.01291.x]
- 11 **Tauras JM**, Palma EC. Venoplasty of innominate bridge dur-ing implantation of single-chamber ICD in a patient with a persistent left-sided superior vena cava. *Pacing Clin Electro-physiol* 2008; **31**: 1077-1078 [PMID: 18684269 DOI: 10.1111/j.1540-8159.2008.01140.x]

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**L-Editor** A **E-Editor** Zhang DN



## A case of type I variant Kounis syndrome with Samter-Beer triad

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**Core tip:** When there is a young individual with no predisposing factors of atherosclerosis and apparent coronary lesion, with or without electrocardiography and biochemical markers of infarction, the possibility of Kounis syndrome should be kept in mind. In such a situation, intracoronary vasodilators, nitrates, nicorandil or diltiazem should be used before proceeding with a coronary intervention. An urgent eosinophil count should be done before proceeding with a coronary intervention to rule out coronary spasm.

Prajapati JS, Virpariya KM, Thakkar AS, Abhyankar AD. A case of type I variant Kounis syndrome with Samter-Beer triad. *World J Cardiol* 2013; 5(4): 112-114 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i4/112.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i4.112>

### Abstract

Kounis syndrome is defined as the coexistence of acute coronary syndromes with situations associated with allergy or hypersensitivity, as well as anaphylactic or anaphylactoid reactions, to a variety of medical conditions, environmental and medication exposures. We report a case of Kounis-Zavras syndrome type I variant in the setting of aspirin-induced asthma, or the Samter-Beer triad of asthma, nasal polyps and aspirin allergy. When there is a young individual with no predisposing factors of atherosclerosis and apparent coronary lesion, with or without electrocardiography and biochemical markers of infarction, the possibility of Kounis syndrome should be kept in mind.

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**Key words:** Kounis syndrome; Samter-Beer triad; Nasal polyps; Coronary spasm; Aspirin allergy

### INTRODUCTION

Kounis syndrome is defined as the coexistence of acute coronary syndromes with situations associated with allergy or hypersensitivity, as well as anaphylactic or anaphylactoid reactions, to a variety of medical conditions, environmental and medication exposures. Patients undergoing stent implantation receive several substances which have anti-genic properties. Many etiologies have been reported<sup>[1,2]</sup>, including drugs (antibiotics, analgesics, antineoplastics, contrast media, corticosteroids, intravenous anesthetics, non-steroidal anti-inflammatory drugs, skin disinfectants, thrombolytics, anticoagulants), various conditions (angio-edema, bronchial asthma, rhinitis, nasal polyp, urticaria, food allergy, exercise-induced allergy, mastocytosis, serum sickness), environmental exposure (stings of ants, bees, wasps and jellyfish, grass cuttings, millet allergy, poisoning, latex contact, eating shellfish, viper venom poisoning) and stent implantation (nickel, chromium, manganese, titanium, molybdenum, polymers), which can induce allergy,

either separately or synergistically<sup>[3]</sup>.

## CASE REPORT

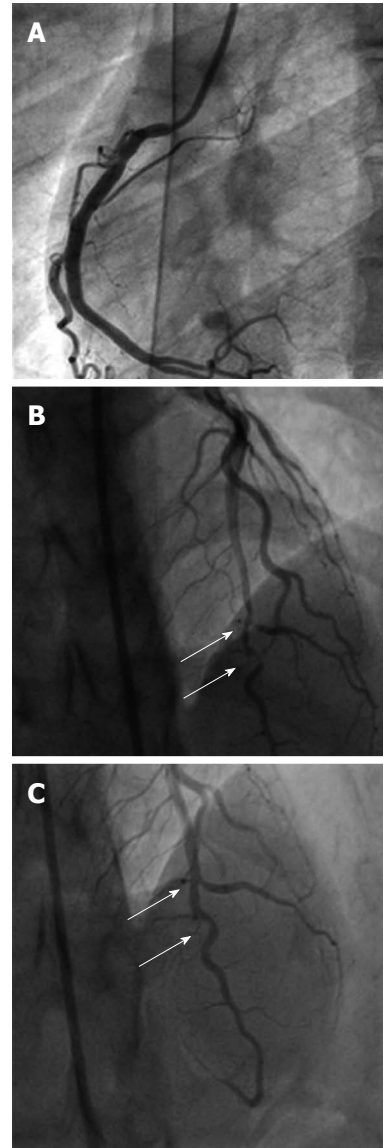
A 19 year old male presented with history of dyspnoea. Over the past 2 d, he had chest pain and the first episode of syncope and was admitted to hospital. On physical examination, he was sweaty but hemodynamically stable. He had no family history of coronary artery disease. Electrocardiography (ECG) showed ventricular tachycardia (VT). On arrival, his Troponin-T was elevated (0.26 ng/mL, reference range: 0-0.03 ng/mL). A diagnosis of non-ST segment myocardial infarction with complete heart block was made. Cardiac catheterization demonstrated 99% lesion in mid right coronary artery (RCA). The ejection fraction was 60%. The percutaneous coronary intervention was performed *via* the right femoral artery access route. A sirolimus-eluting stent (3.5 mm × 23 mm) was deployed with an excellent angiographic result. The patient was discharged on the fifth day.

Two months later, the patient was again hospitalized with a second episode of syncope arrest and chest pain. In the brain magnetic resonance image, no significant focal intracranial abnormality was detected. An absolute eosinophil count was 645 cumm/ $\mu$ L (reference range: 40-440 cumm/ $\mu$ L). Check angiogram revealed a well flowing RCA stent with 40% *de novo* lesion. The remaining coronary arteries were normal. The patient was recommended for medical management and was discharged on the seventh day.

Five months later, the patient had a 3<sup>rd</sup> episode of syncope, and hence was rehospitalized for clinical evaluation with twenty-four hour electrocardiographic (Holter) monitoring, which was normal. At this time, ECG and echocardiography were normal. Patient developed VT during hospitalization which was reverted with direct current shock and beta blockers were started. During the hospital stay, on the 3<sup>rd</sup> day, the patient had chest pain again. Troponin-I was positive. A 12-lead electrocardiogram showed ST elevation in anterior leads, suggestive of hyper acute stage of anterior wall myocardial infarction. The patient was transferred to the intensive cardiac care unit and there the ST elevation disappeared. Echocardiography showed mid apical septum and apex hypokinesia. Glycoprotein IIb/IIIa inhibitors were given.

## DISCUSSION

When the fourth check angiography was done, it revealed a mid to distal left anterior descending (LAD) 90% discrete lesion with sluggish flow and a well flowing RCA stent. The patient was taken for percutaneous transluminal coronary angioplasty (PTCA) to LAD after 3 d. During coronary angiography, prior to PTCA, another 80% lesion proximal to previous 90% lesion was revealed where previously no plaque was present. After repeated administered nicorandil and nitrates, both lesions became insignificant. Hence, we suspect it might due to coronary



**Figure 1** Angiographic images. A: Well flowing patent right coronary artery; B: Angiography revealed mid left anterior descending (LAD) two consecutive lesions (arrows) at D2 bifurcation; C: After *iv* nicorandil and nitroglycerin, mid LAD lesions (arrows) at D2 bifurcation.

spasm. The patient was discharged under treatment with oral nicorandil, nitrates, diltiazem and antiplatelets. Beta blockers were omitted (Figure 1).

After discharge, patient had difficulty in breathing due to some nasal obstruction, so an Ear Nose and Throat (ENT) surgeon consultation was done. Subsequently, a nasal ethmoidal polyp was detected by the ENT surgeon on the basis of a computed tomography scan. The chest physician's opinion was taken and pulmonary function tests were done, which were suggestive of mild obstructive lung disease. Bilateral functional endoscopic sinus surgery was also done (3.5 cm × 2.5 cm, reference range: 0.2 cm × 0.2 cm up to 1.4 cm × 0.8 cm). The histopathological examination of polyps was suggestive of inflammatory nasal polyps. An immunoglobulin E level was 396 kU/L (reference range: 20-100 kU/L). Normal range for

all allergens is less than 0.35 U/L. Within food, cucumber 1.70 U/L, wheat 2.00 U/L, groundnut 1.80 U/L and yeast 1.60 U/L induce mid high allergy. Within inhalants, house dust 1.90 U/L, dog dander 1.10 U/L and paper dust 1.10 U/L induce mid high allergy, while house dust mite 3.50 U/L induces high allergy. Within contact, perfume 1.40 U/L induces mid high allergy. Within drugs, ciprofloxacin 1.70 U/L, cloxacillin 1.30 U/L and diclofenac 1.10 U/L induce mid high allergy, while oxacillin 0.90 U/L, tetracycline 0.60 U/L and norfloxacin 0.80 U/L induce mild allergy. During allergic screening tests (by immune-enzyme immune assay), it was found that the patient was allergic to contact, drugs, food and inhalants. The patient was advised to avoid these allergens and put on topical steroids, cetirizine and montelukast. Aspirin was omitted. To date, the patient has been doing well for the last 9 mo.

Today, allergic angina and allergic myocardial infarction are referred as “Kounis syndrome”. Aspirin-induced asthma was first described by Widal *et al* in 1922 and later by Samter *et al*<sup>[4]</sup> in 1967. The term Samter’s triad (asthma, aspirin sensitivity and nasal polyps) became popular. The Samter-Beer triad generally starts as chronic rhinitis with development of nasal polyposis. Salicylate intolerance and asthma develop over 1 to 5 years<sup>[5]</sup>.

When there is a young individual with no predisposing factors of atherosclerosis and apparent coronary le-

sion, with or without ECG and biochemical markers of infarction, the possibility of Kounis syndrome should be kept in mind. In such situations, intracoronary vasodilators, nitrates, nicorandil or diltiazem should be used before proceeding with a coronary intervention. An urgent eosinophil count should be done before proceeding with coronary interventions to rule out coronary spasm.

## REFERENCES

- 1 **Yanagawa Y**, Nishi K, Tomiharu N, Kawaguchi T. A case of takotsubo cardiomyopathy associated with Kounis syndrome. *Int J Cardiol* 2009; **132**: e65-e67 [PMID: 18031840 DOI: 10.1016/j.ijcard.2007.08.022]
- 2 **Kounis GN**, Kounis SA, Hahalis G, Kounis NG. Coronary artery spasm associated with eosinophilia: another manifestation of Kounis syndrome? *Heart Lung Circ* 2009; **18**: 163-164 [PMID: 19081300 DOI: 10.1016/j.hlc.2008.09.008]
- 3 **Chen JP**, Hou D, Pendyala L, Goudevenos JA, Kounis NG. Drug-eluting stent thrombosis: the Kounis hypersensitivity-associated acute coronary syndrome revisited. *JACC Cardiovasc Interv* 2009; **2**: 583-593 [PMID: 19628178 DOI: 10.1016/j.jcin.2009.04.017]
- 4 **Samter M**, Beers RF. Concerning the nature of intolerance to aspirin. *J Allergy* 1967; **40**: 281-293 [PMID: 5235203 DOI: 10.1016/0021-8707(67)90076-7]
- 5 **Szczeklik A**, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000; **16**: 432-436 [PMID: 11028656]

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## Evaluation of myocardial infarction patients after coronary revascularization by dual-phase multi-detector computed tomography: Now and in future

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### Abstract

Multidetector-row computed tomography (MDCT) has become one of the major tools in diagnosing and evaluating patients with coronary artery disease in recent years. In selected patients, MDCT has been shown to provide more reliable accuracy in detection of stent patency than invasive coronary angiography. Chiou *et al* reported a delicate infarcted myocardium at-risk score. According to their results, the MDCT-based myocardium at-risk score had a good correlation with the thallium 201 ST-segment elevation myocardial infarction-based summed difference score ( $r = 0.841$ ,  $P < 0.001$ ). They claimed that dual-phase MDCT is useful in detecting different patterns of obstructive lesions and the extent

of myocardium at risk. In this commentary, we discuss the current status of the clinical application of MDCT in patients with myocardial infarction in relation to evaluating the myocardial perfusion defect, detecting reversible myocardial ischemia, assessing myocardial viability, estimating target lesion restenosis, and calculating of fractional flow reserve from MDCT.

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**Key words:** Coronary artery disease; Fractional flow reserve; Multidetector-row computed tomography; Myocardial infarction

**Core tip:** Chiou *et al* reported that dual-phase multidetector-row computed tomography (MDCT) is useful in detecting different patterns of obstructive lesions and the extent of myocardium at risk. In this commentary, we discuss the current status of the clinical application of MDCT in patients with myocardial infarction in relation to evaluating the myocardial perfusion defect, detecting reversible myocardial ischemia, assessing myocardial viability, estimating target lesion restenosis, and calculating of fractional flow reserve from MDCT.

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### TO THE EDITOR

We have read the recent published article by Chiou *et al*<sup>[1]</sup> which reported that the dual-phase multidetector-row computed tomography (MDCT) is useful in detecting dif-

ferent patterns of obstructive lesions and the extent of myocardium at risk in patients with ST-segment elevation myocardial infarction (STEMI). We think that this article is interesting and would strongly recommend it to readers.

With its rapid advancement in recent years, MDCT has become one of the major tools in diagnosing and evaluating patients with coronary artery disease. The high negative predictive rate has made MDCT a powerful tool in excluding occlusive coronary lesions in symptomatic patients with low probability of disease<sup>[2,3]</sup>. In selected patients, MDCT has also been shown to provide more reliable accuracy in detection of stent patency than invasive coronary angiography<sup>[4]</sup>. Chiou *et al.*<sup>[1]</sup> reported a delicate infarcted myocardium at-risk score. According to their results from 135 ST-segment elevation myocardial infarction (STEMI) patients with recurrent symptoms 9 mo after revascularization and analysis of 1966 segments, the myocardium at-risk score has higher sensitivity, specificity, and positive- and negative-predictive values (98.7%, 76.1%, 87.5%, and 97.2% respectively) than analysis from stress-redistribution thallium-201 SPECT plus invasive coronary angiography. In 124 (91.9%) patients in whom all segments were assessable, the MDCT-based myocardium at-risk score had a good correlation with the SPECT-based summed difference score (SDS) ( $r = 0.841$ ,  $P < 0.001$ ). With a cutoff value of 2.68, the area under the receiver operating characteristic curve was 0.874 (95%CI: 0.805-0.942) for the MDCT-based infarcted myocardium at-risk score<sup>[1]</sup>. Although additional studies with a larger population are required, MDCT-based risk stratification has been shown to be a promising noninvasive tool with good correlation to the current standard for evaluating obstructive lesions and the severity of the myocardium at risk in patients with STEMI who develop recurrent symptoms.

Correct identification of flow-limiting coronary artery stenosis is the cornerstone of interventional treatment in patients with ischemic angina<sup>[5]</sup>. However, the correlation of morphological severity with myocardial blood flow reduction is low<sup>[6]</sup>.

Functional studies with nuclear myocardial imaging, including SPECT and positron emission tomography, are the current major modalities<sup>[7]</sup>, but attenuation artifacts, high radiation dose and prolonged examination time limit the clinical benefits. Several computed tomography (CT) techniques have been developed to evaluate the myocardial blood supply<sup>[5]</sup>. During the early phase of contrast medium passage through the myocardium, perfusion defects can be delineated by analysis of reconstruction images based on systolic and diastolic cycles<sup>[8,9]</sup> and optimal timing of first-pass scans<sup>[10]</sup>. Dual source CT reduces beam-hardening artifacts significantly by use of monochromatic image handling technology, and further improves the accuracy of myocardial perfusion quantification<sup>[11]</sup>. Dynamic time phases may be useful in prediction of myocardial perfusion defects<sup>[12]</sup>, which may be related to left ventricular functional recovery in patients with

acute myocardial infarction<sup>[13]</sup>. Injection of adenosine before scanning has also been an well-accepted pharmacological stress method for detecting reversible myocardial ischemia<sup>[14]</sup>.

The other important action during the planning of coronary revascularization is to estimate myocardial viability and predict the possible recovery of ventricular function<sup>[15]</sup>. Differential contrast enhancement of infarcted myocardial tissue was initially recognized on CT images and was also reported for gadolinium-enhanced cardiac magnetic resonance imaging (MRI). In the normal condition, the iodinated and gadolinium contrast medium distribute through the cardiac extracellular space but are excluded from healthy myocardial cells. After ischemic injury, differences in distribution volume occurring after loss of myocardial membrane integrity enable delayed gadolinium-enhanced MRI to define the periinfarction area of edema and the central core of necrosis<sup>[16,17]</sup>. In a study of preoperative evaluation before coronary artery bypass surgery, the extent of delayed transmural hyperenhancement in MRI images has been shown to have strong correlation with the recovery of regional ventricular function after 6 mo<sup>[18]</sup>. In the acute myocardial infarction, delayed-enhancement MRI also provides prediction of recovery of function after successful primary angioplasty by analysis of microvascular obstruction<sup>[19]</sup>. Assessment of myocardial viability using MDCT has been validated by a number of studies. The detection of periinfarction edema<sup>[20]</sup> and nonreperfused area<sup>[21]</sup> in the setting of acute myocardial infarction was shown to have good correlation with MRI imaging and myocardial histological staining. In a recent study, myocardial contrast delayed enhancement of MDCT was shown to be well correlated with nonviable myocardium and a significant independent predictor of clinical outcome<sup>[22]</sup>. The viability evaluation of myocardium by CT is still under verification. However, CT warrants a future role in this area as it is less time-consuming and patient-limiting than MRI<sup>[5]</sup>.

Recently, a novel method of calculation of fractional flow reserve (FFR) from MDCT has been reported<sup>[23]</sup>. FFR is the ratio of the mean coronary pressure distal to a stenotic coronary lesion to the mean aortic pressure, as measured during invasive coronary angiography<sup>[24]</sup>. FFR has been shown to have greater accuracy than exercise electrocardiography, myocardial perfusion scintigraphy, and stress echocardiography in determination of hemodynamically significant stenoses<sup>[25]</sup>. Advancement of technology has enables calculation of FFR from MDCT without additional imaging, change of MDCT protocols, or pharmacological administration<sup>[23,26]</sup>. In other words, FFR derived from coronary computed tomography is a noninvasive method for diagnosis of lesion-specific ischemia. From the initial data published to date<sup>[19,27]</sup>, use of noninvasive FFR from MDCT for patients with suspected coronary artery disease improves diagnostic accuracy in comparison with MDCT alone. In a recently published multicenter international study, FFR from MDCT showed a diagnostic accuracy, sensitivity, specificity value

of 73%, 90%, and 54%, respectively, on a per-patient basis compared to traditionally invasive FFR<sup>[23]</sup>. In another study, a good correlation was shown between per-vessel FFR from MDCT and invasive FFR values (Spearman's rank correlation = 0.717,  $P < 0.0001$ ; Pearson's correlation coefficient = 0.678,  $P < 0.0001$ )<sup>[28]</sup>. Calculations of FFRs from MDCT were performed by computational fluid dynamic modeling after semiautomated segmentation of coronary arteries and left ventricular mass. This process currently requires approximately 6 h per case<sup>[23]</sup>. With further improvement of the computation technology, we believe that the processing time will be much shorter, making it feasible for clinical use in the near future.

Noninvasive identification of the patency of culprit vessels remains a challenging issue in patients of STEMI. We and others have reported that MDCT could accurately and safely identify occluded culprit lesions in patients early after acute myocardial infarction (AMI), which may provide important information to aid in risk stratification<sup>[29,30]</sup>. In patients with acute coronary syndrome showing ambiguous ST segment changes on electrocardiogram, MDCT adds diagnostic accuracy and helps to exclude pulmonary embolism, aortic dissection, and other thoracic disease<sup>[31]</sup>. For patients with complex coronary artery disease who require bypass surgery, the 3D-image reconstruction from MDCT also provides additional details to operators<sup>[32]</sup>. Furthermore, it has been reported that the myocardial viability assessment derived from MDCT after primary revascularization may help to predict the clinical outcome in patients with AMI<sup>[22]</sup>.

In summary, the evaluation of STEMI patients with recurrence of chest symptoms remains a challenge. Utilization of state-of-the-art MDCT for delayed myocardial enhancement and calculation of infarcted myocardium at-risk score helps therapeutic planning and risk stratification. In the near future, we believe that the FFR obtained from MDCT may also contribute to coronary ischemia assessment.

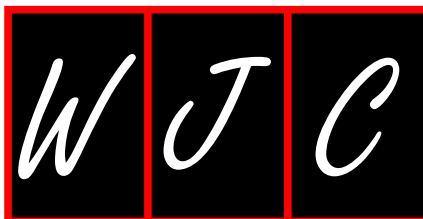
## REFERENCES

- 1 **Chiou KR**, Peng NJ, Hsiao SH, Huang YL, Cheng CC, Pan HB, Wu MT. CT of coronary heart disease: Part 2, Dual-phase MDCT evaluates late symptom recurrence in ST-segment elevation myocardial infarction patients after revascularization. *AJR Am J Roentgenol* 2012; **198**: 548-562 [PMID: 22357993 DOI: 10.2214/AJR.11.7072]
- 2 **Taylor AJ**, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD, Kramer CM, Berman D, Brown A, Chaudhry FA, Cury RC, Desai MY, Einstein AJ, Gomes AS, Harrington R, Hoffmann U, Khare R, Lesser J, McGann C, Rosenberg A, Schwartz R, Shelton M, Smetana GW, Smith SC. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular
- 3 **Angiography and Interventions**, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010; **56**: 1864-1894 [PMID: 21087721 DOI: 10.1016/j.jacc.2010.07.005]
- 3 **Arbab-Zadeh A**, Hoe J. Quantification of coronary arterial stenoses by multidetector CT angiography in comparison with conventional angiography methods, caveats, and implications. *JACC Cardiovasc Imaging* 2011; **4**: 191-202 [PMID: 21329905 DOI: 10.1016/j.jcmg.2010.10.011]
- 4 **Carrabba N**, Schuijf JD, de Graaf FR, Parodi G, Maffei E, Valenti R, Palumbo A, Weustink AC, Mollet NR, Accetta G, Cademartiri F, Antoniucci D, Bax JJ. Diagnostic accuracy of 64-slice computed tomography coronary angiography for the detection of in-stent restenosis: a meta-analysis. *J Nucl Cardiol* 2010; **17**: 470-478 [PMID: 20379863 DOI: 10.1007/s12350-010-9218-2]
- 5 **Vliegenthart R**, Henzler T, Moscariello A, Ruzsics B, Bastarika G, Oudkerk M, Schoepf UJ. CT of coronary heart disease: Part 1, CT of myocardial infarction, ischemia, and viability. *AJR Am J Roentgenol* 2012; **198**: 531-547 [PMID: 22357992 DOI: 10.2214/AJR.11.7082]
- 6 **Kern MJ**, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 2010; **55**: 173-185 [PMID: 20117397 DOI: 10.1016/j.jacc.2009.06.062]
- 7 **Klocke FJ**, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO, Cerqueira MD, St John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 2003; **108**: 1404-1418 [PMID: 12975245 DOI: 10.1161/01.CIR.0000080946.42225.4D]
- 8 **Hoffmann U**, Millea R, Enzweiler C, Ferencik M, Gulick S, Titus J, Achenbach S, Kwait D, Sosnovik D, Brady TJ. Acute myocardial infarction: contrast-enhanced multi-detector row CT in a porcine model. *Radiology* 2004; **231**: 697-701 [PMID: 15118118 DOI: 10.1148/radiol.2313030132]
- 9 **Nagao M**, Matsuoka H, Kawakami H, Higashino H, Mochizuki T, Murase K, Uemura M. Quantification of myocardial perfusion by contrast-enhanced 64-MDCT: characterization of ischemic myocardium. *AJR Am J Roentgenol* 2008; **191**: 19-25 [PMID: 18562719 DOI: 10.2214/AJR.07.2929]
- 10 **Bischoff B**, Bamberg F, Marcus R, Schwarz F, Becker HC, Becker A, Reiser M, Nikolaou K. Optimal timing for first-pass stress CT myocardial perfusion imaging. *Int J Cardiovasc Imaging* 2013; **29**: 435-442 [PMID: 22714549]
- 11 **So A**, Hsieh J, Imai Y, Narayanan S, Kramer J, Procknow K, Dutta S, Leipsic J, Min JK, Labounty T, Lee TY. Prospectively ECG-triggered rapid kV-switching dual-energy CT for quantitative imaging of myocardial perfusion. *JACC Cardiovasc Imaging* 2012; **5**: 829-836 [PMID: 22897997 DOI: 10.1016/j.jcmg.2011.12.026]
- 12 **Ko SM**, Kim YW, Han SW, Seo JB. Early and delayed myocardial enhancement in myocardial infarction using two-phase contrast-enhanced multidetector-row CT. *Korean J Radiol* 2007; **8**: 94-102 [PMID: 17420626]
- 13 **Koyama Y**, Matsuoka H, Mochizuki T, Higashino H, Kawakami H, Nakata S, Aono J, Ito T, Naka M, Ohashi Y, Higaki J. Assessment of reperfused acute myocardial infarction with two-phase contrast-enhanced helical CT: prediction of left ventricular function and wall thickness. *Radiology* 2005; **235**: 804-811 [PMID: 15833978 DOI: 10.1148/radiol.2353030441]
- 14 **Rocha-Filho JA**, Blankstein R, Shturman LD, Bezerra HG, Okada DR, Rogers IS, Ghoshhajra B, Hoffmann U, Feuchtnner G, Mamuya WS, Brady TJ, Cury RC. Incremental value of

- adenosine-induced stress myocardial perfusion imaging with dual-source CT at cardiac CT angiography. *Radiology* 2010; **254**: 410-419 [PMID: 20093513 DOI: 10.1148/radiol.09091014]
- 15 **Arai AE**. The cardiac magnetic resonance (CMR) approach to assessing myocardial viability. *J Nucl Cardiol* 2011; **18**: 1095-1102 [PMID: 21882082]
- 16 **Wendland MF**, Saeed M, Arheden H, Gao DW, Canet E, Bremerich J, Dae MW, Higgins CB. Toward necrotic cell fraction measurement by contrast-enhanced MRI of reperfused ischemically injured myocardium. *Acad Radiol* 1998; **5** Suppl 1: S42-S44; discussion S42-S44 [PMID: 9561040]
- 17 **Ordovas KG**, Higgins CB. Delayed contrast enhancement on MR images of myocardium: past, present, future. *Radiology* 2011; **261**: 358-374 [PMID: 22012903 DOI: 10.1148/radiol.11091882]
- 18 **Selvanayagam JB**, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, Neubauer S. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation* 2004; **110**: 1535-1541 [PMID: 15353496 DOI: 10.1161/01.CIR.0000142045.22628.74]
- 19 **Baks T**, van Geuns RJ, Biagini E, Wielopolski P, Mollet NR, Cademartiri F, van der Giessen WJ, Krestin GP, Serruys PW, Duncker DJ, de Feyter PJ. Effects of primary angioplasty for acute myocardial infarction on early and late infarct size and left ventricular wall characteristics. *J Am Coll Cardiol* 2006; **47**: 40-44 [PMID: 16386662 DOI: 10.1016/j.jacc.2005.09.008]
- 20 **Mahnken AH**, Bruners P, Bornikoeel CM, Krämer N, Guenther RW. Assessment of myocardial edema by computed tomography in myocardial infarction. *JACC Cardiovasc Imaging* 2009; **2**: 1167-1174 [PMID: 19833305 DOI: 10.1016/j.jcmg.2009.05.014]
- 21 **Buecker A**, Katoh M, Krombach GA, Spuentrup E, Bruners P, Günther RW, Niendorf T, Mahnken AH. A feasibility study of contrast enhancement of acute myocardial infarction in multislice computed tomography: comparison with magnetic resonance imaging and gross morphology in pigs. *Invest Radiol* 2005; **40**: 700-704 [PMID: 16230902 DOI: 10.1097/01.rli.0000179524.58411.a2]
- 22 **Sato A**, Nozato T, Hikita H, Akiyama D, Nishina H, Hoshi T, Aihara H, Kakefuda Y, Watabe H, Hiroe M, Aonuma K. Prognostic value of myocardial contrast delayed enhancement with 64-slice multidetector computed tomography after acute myocardial infarction. *J Am Coll Cardiol* 2012; **59**: 730-738 [PMID: 22340265 DOI: 10.1016/j.jacc.2011.10.890]
- 23 **Min JK**, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, Erglis A, Lin FY, Dunning AM, Apruzzese P, Budoff MJ, Cole JH, Jaffer FA, Leon MB, Malpeso J, Mancini GB, Park SJ, Schwartz RS, Shaw LJ, Mauri L. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012; **308**: 1237-1245 [PMID: 22922562]
- 24 **Pijls NH**, De Bruyne B. Coronary pressure measurement and fractional flow reserve. *Heart* 1998; **80**: 539-542 [PMID: 10065019]
- 25 **Pijls NH**, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; **334**: 1703-1708 [PMID: 8637515 DOI: 10.1056/NEJM199606273342604]
- 26 **Kim HJ**, Vignon-Clementel IE, Coogan JS, Figueroa CA, Jansen KE, Taylor CA. Patient-specific modeling of blood flow and pressure in human coronary arteries. *Ann Biomed Eng* 2010; **38**: 3195-3209 [PMID: 20559732 DOI: 10.1007/s10439-010-0083-6]
- 27 **Min JK**, Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning AM, Defrance T, Lansky A, Leipsic J. Usefulness of noninvasive fractional flow reserve computed from coronary computed tomographic angiograms for intermediate stenoses confirmed by quantitative coronary angiography. *Am J Cardiol* 2012; **110**: 971-976 [PMID: 22749390 DOI: 10.1016/j.amjcard.2012.05.033]
- 28 **Koo BK**, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 2011; **58**: 1989-1997 [PMID: 22032711 DOI: 10.1016/j.jacc.2011.06.066]
- 29 **Huang WC**, Chiou KR, Liu CP, Lin SK, Huang YL, Mar GY, Lin SL, Wu MT. Multidetector row computed tomography can identify and characterize the occlusive culprit lesions in patients early (within 24 hours) after acute myocardial infarction. *Am Heart J* 2007; **154**: 914-922 [PMID: 17967598 DOI: 10.1016/j.ahj.2007.07.002]
- 30 **Shabestari AA**, Akhlaghpour S, Tayebivaljozi R, Fattahi Masrouf F. Prevalence of Congenital Coronary Artery Anomalies and Variants in 2697 Consecutive Patients Using 64-Detector Row Coronary CT Angiography. *Iran J Radiol* 2012; **9**: 111-121 [PMID: 23329976 DOI: 10.5812/iranjradiol.8070]
- 31 **Takakuwa KM**, Halpern EJ. Evaluation of a "triple rule-out" coronary CT angiography protocol: use of 64-Section CT in low-to-moderate risk emergency department patients suspected of having acute coronary syndrome. *Radiology* 2008; **248**: 438-446 [PMID: 18641247 DOI: 10.1148/radiol.2482072169]
- 32 **Tresoldi S**, Mezzanzanica M, Campari A, Salerno Uriarte D, Cornalba G. The role of computed tomography coronary angiography in the management of coronary anomalies. *J Card Surg* 2013; **28**: 33-36 [PMID: 23241033 DOI: 10.1111/jocs.12040]

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## GENERAL INFORMATION

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*WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

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- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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