ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2021 November 26; 13(11): 599-649

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 13 Number 11 November 26, 2021

OPINION REVIEW

REVIEW

MINIREVIEWS

World Journal of Cardiology

Monthly Volume 13 Number 11 November 26, 2021

Contents

NAME OF JOURNAL

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE

November 26, 2021

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS

https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 November 26; 13(11): 599-607

DOI: 10.4330/wjc.v13.i11.599

ISSN 1949-8462 (online)

OPINION REVIEW

Safety and efficacy of dual antiplatelet therapy after percutaneous coronary interventions in patients with end-stage liver disease

Zvonimir Ostojic, Ana Ostojic, Josko Bulum, Anna Mrzljak

ORCID number: Zvonimir Ostojic 0000 0003 1762 9270; Ana Ostojic 0000-0003-4234-4461; Josko Bulum 0000 0002 1482 6503; Anna Mrzljak 0000-0001-6270-2305.

Author contributions: Ostojic Z and Ostojic A made contributions to the conception and design of the study, collected the data and drafted the manuscript; Bulum J and Mrzljak A revised the manuscript critically; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict interest.

Country/Territory of origin: Croatia

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Zvonimir Ostojic, Department of Cardiology, University Clinical Hospital Zagreb, Zagreb 10000, Croatia

Ana Ostojic, Anna Mrzljak, Department of Gastroenterology and Hepatology, University Hospital Center, Zagreb 10000, Croatia

Josko Bulum, Department of Cardiovascular Diseases, University Hospital Center Zagreb, University Clinical Hospital Zagreb, Zagreb 10000, Croatia

Josko Bulum, Anna Mrzljak, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Corresponding author: Ana Ostojic, MD, PhD, Senior Postdoctoral Fellow, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, Kispaticeva 12, Zagreb 10000, Croatia. ostojicana.zg@gmail.com

Abstract

The prevalence of coronary artery disease (CAD) increases in patients with end-stage liver disease, with part of them receiving the percutaneous coronary intervention (PCI) as a treatment option. Dual antiplatelet therapy (DAPT), a standard of care after PCI, could result in catastrophic consequences in this population. Before PCI and the start of DAPT, it is recommended to assess patient bleeding risk. Based on novel findings, liver cirrhosis does not necessarily lead to a significant increase in bleeding complications. Furthermore, conventional methods, such as the international normalized ratio, might not be appropriate in assessing individual bleeding risk. The highest bleeding risk among cirrhotic patients has a subgroup with severe thrombocytopenia ($< 50 \times 10^9$/L) and elevated portal pressure. Therefore, every effort should be made to maintain thrombocyte count above $> 50 \times 10^9$/L and prevent variceal bleeding. There is no solid evidence for DAPT in patients with cirrhosis. However, randomized trials investigating short (one month) DAPT duration after PCI with new drug-eluting stents (DES) in a high bleeding risk patient population can be implemented in patients with cirrhosis. Based on retrospective studies (with older stents and protocols), PCI and DAPT appear to be safe but with a higher risk of bleeding complications with longer DAPT usage. Finally, novel methods in assessing CAD severity should be performed to avoid unnecessary PCI and potential risks associated with DAPT. When indicated, PCI should be performed over radial artery using contemporary DES. Complementary medical therapy, such as proton pump inhibitors and beta-blockers, should be prescribed for lower bleeding risk patients. Novel approaches, such as thromboelastography and "preventive"

Received: March 23, 2021
Peer-review started: March 23, 2021
First decision: July 30, 2021
Revised: August 6, 2021
Accepted: October 25, 2021
Article in press: October 25, 2021
Published online: November 26, 2021

P-Reviewer: Gadour E
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

upper endoscopies in PCI circumstances, warn clinical confirmation.

Key Words: End-stage liver disease; Cirrhosis; Liver transplantation; Coronary artery disease; Percutaneous coronary intervention; Antiplatelet therapy

Core Tip: Dual antiplatelet therapy (DAPT) is necessary after a percutaneous coronary intervention (PCI). However, it could result in severe consequences in patients with liver cirrhosis. Based on novel findings, liver cirrhosis does not necessarily lead to a significant increase in bleeding complications. Patients with cirrhosis who have the highest bleeding risk are those with severe thrombocytopenia and elevated portal pressure. Despite the lack of solid evidence for DAPT in patients with cirrhosis, trials investigating one month of DAPT duration after PCI can be implemented in cirrhotic patients. Before PCI, functional assessment of coronary artery disease severity should be performed to avoid unnecessary interventions.

Citation: Ostojic Z, Ostojic A, Bulum J, Mrzljak A. Safety and efficacy of dual antiplatelet therapy after percutaneous coronary interventions in patients with end-stage liver disease. *World J Cardiol* 2021; 13(11): 599-607
URL: https://www.wjgnet.com/1949-8462/full/v13/i11/599.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i11.599

INTRODUCTION

The prevalence of coronary artery disease (CAD) in patients with liver cirrhosis is estimated from 20% to 26%[1-3]. Furthermore, due to the growing incidence of cirrhosis caused by non-alcoholic fatty liver disease, which has overlapping risk factors with the CAD, an even higher prevalence of CAD in patients with cirrhosis can be expected[4,5]. The presence of both comorbidities can limit treatment options for each. For example, a patient can be rejected for surgical heart revascularization due to high operative risk or for the potential liver transplantation (LT) due to unresolved CAD. Percutaneous coronary intervention (PCI) with stent implantation represents a valid treatment option for CAD[6]. Data from the United States report that 1.2% of patients undergoing PCI have cirrhosis[7]. However, dual antiplatelet therapy (DAPT), a standard of care after stent implantation, can have severe consequences in cirrhotic patients with cirrhosis due to elevated bleeding risk.

This article aims to define; do all patients with liver cirrhosis have the same bleeding risk, the evidence behind DAPT in patients with cirrhosis, and what can be done to lower bleeding risk in such patients.

ARE ALL PATIENTS WITH CIRRHOSIS AT THE SAME RISK OF BLEEDING?

In the past, all patients with liver cirrhosis were classified as having high bleeding risk (HBR) due to coagulation abnormalities, thrombocytopenia, and elevated portal pressure-related complications. However, these presumptions are changing with growing evidence that, at least, part of patients with cirrhosis might have a high thrombotic risk[8,9]. Complex alterations in the hemostatic system cause so-called rebalanced hemostasis, meaning that impaired protein synthesis leads to a decreased level of procoagulant factors and anticoagulant factors[10,11]. The international normalized ratio (INR) is often used as a parameter for coagulation cascade competence in cirrhosis, although primarily invented for the warfarin dosing and not for the above mentioned[9]. The potential problem arises from the fact that it measures procoagulant factors but not anticoagulant factors such as protein C and S, which are also depleted in patients with liver cirrhosis[9,12]. Furthermore, it does not measure Factor VIII, whose levels are elevated in cirrhosis patients due to its endothelial

production[13]. Finally, studies that tried to "correct" INR using fresh frozen plasma or activated Factor VII, failed to reduce bleeding events[14-17]. Additionally, fibrinogen measurement has been proposed as a potential alternative to INR for assessing bleeding risk, although its clinical usefulness is yet to be confirmed[9].

The second risk factor for bleeding in patients with cirrhosis is thrombocytopenia, occurring in 64%-84% of patients with cirrhosis or fibrosis[18]. Its cause is multifactorial, with the most important being decreased production due to depressed thrombopoietin levels, splenic sequestration, and increased destruction[9,19-21]. However, a platelet count of > 50 × 10^9/L has been shown to be sufficient to maintain thrombin generation in *in vitro* studies[8,21-23]. This cut level has been recognized by McCarthy *et al*[24] in their opinion paper on management of DAPT in patients with thrombocytopenia, where they advise avoiding PCI in case of thrombocyte count < 50 × 10^9/L. Furthermore, in cirrhotic patients, platelet-induced anticoagulation changes are counterbalanced with the higher activity of endothelium-derived von Willebrand factor[8,9,25].

The third risk factor for bleeding in patients with cirrhosis are complications arising from portal hypertension, primarily esophageal varices[26,27]. The risk of variceal hemorrhage is related to variceal size, the severity of liver dysfunction (Child-Pugh B/C), and the presence of red wale marks on varices[28]. This issue had been recognized in a consensus document from Academic Research Consortium for High Bleeding Risk, in which they defined patients with cirrhosis and portal hypertension as having HBR after PCI[29]. Of note, in the same document, patients with thrombocytopenia (defined as < 100 × 10^9/L), irrespective of etiology, and those with chronic bleeding diathesis are likewise defined as having HBR. Finally, it is essential to emphasize there is no valid bleeding risk score for patients with liver cirrhosis. Most used Child-Pugh and Mayo End-Stage Liver Disease criteria are developed for predicting mortality and not bleeding events, despite having INR as an integrative part of both[30-32]. In summary, based on presented data, patients with the highest bleeding risk are those with severe thrombocytopenia (< 50 × 10^9/L) and those with portal hypertension.

WHAT IS THE CURRENT EVIDENCE REGARDING DAPT AFTER PCI IN PATIENTS WITH CIRRHOSIS?

Historically, due to the concerns for late stent thrombosis after drug-eluting stent (DES) implantation, DAPT was recommended for 12 mo after such procedures. Thus, patients with HBR, including those with liver disease, were excluded from most modern DES trials[29]. Therefore, implantation of a bare-metal stent (BMS) followed by one month of DAPT was recommended in those cases[29]. However, with DES technology advancements and stent thrombosis reduction, randomized trials in HBR patients have been performed. In the LEADERS FREE trial, almost 2500 patients were allocated to modern DES or BMS, followed by one month of DAPT. After one year of follow-up, DES implantation was superior to BMS concerning primary safety endpoint [a composite of cardiac death, myocardial infarction (MI), or stent thrombosis] [9.4% *vs* 12.9%; hazard ratio, 0.71; 95% confidence interval (CI): 0.56-0.91; P < 0.001 for noninferiority and P = 0.005 for superiority] with the lower incidence of clinically driven target lesion revascularization (5.1% *vs* 9.8%; hazard ratio, 0.50; 95%CI: 0.37-0.69; P < 0.001)[33]. Similarly, in ONYX ONE trial, which included 1996 patients, DES implantation was non-inferior to BMS (both with one month of DAPT) after one year of follow-up[34]. Even though both trials investigated patients with HBR, the prevalence of patients with liver disease/cirrhosis was < 1%, too small to extract conclusions in this patient population[33,34].

Several retrospective studies described and investigated outcomes after PCI in patients with liver cirrhosis compared to different patient populations, with only one of them more focused on antiplatelet management[4,7,35-38]. The largest of them was conducted by Wu *et al*[35], which included 914 cirrhotic patients who underwent PCI due to MI and compared them to a four times larger propensity-matched group of patients without cirrhosis. The cirrhosis group had significantly higher 1-year mortality (32.7% *vs* 23.7%, 95%CI: 1.28-1.74) but less recurrent MIs (6.0% *vs* 8.7%, 95%CI: 0.54-0.92). Importantly, cirrhosis group had non-significant increase in major bleeding (3.7% *vs* 2.9%, 95%CI: 0.87-1.23) and significantly increased gastrointestinal bleeding (28.0% *vs* 20.2%, 95%CI: 1.31-1.70). A sub-analysis showed significantly lower mortality and non-significant decreases in recurrent MI in the DAPT subgroup (duration of DAPT had to be > 3 mo) compared to cirrhotic patients on a single

antiplatelet agent. However, patients with a single antiplatelet agent were significantly older with significantly more severe comorbidities (such as heart failure and history of gastrointestinal bleeding), so direct comparison is questionable[35]. After PCI in patients with cirrhosis, worse in-hospital mortality than a historic non-cirrhotic group has also been described by Singh *et al*[7]. In the same study, patients with cirrhosis had worse outcomes if they received BMS instead of DES[7].

The two studies comparing PCI and medical therapy in CAD patients with cirrhosis found no difference in 1-year mortality and a higher bleeding rate[36,37]. Importantly, Krill *et al*[36] described a temporal change in bleeding events. The difference in bleeding was non-significantly different at 30- and 90-d follow-up (although higher in the PCI group) but become significant after 1 and 2 years. That might be associated with higher and extended use of DAPT in the PCI group (63% of patients had DAPT 1 year after PCI)[36]. Similarly, Russo *et al*[4] and Azarbal *et al*[38] described no significant difference in bleeding after PCI than medical therapy, although higher in the PCI group, in shorter follow up of 11 and 1 mo, respectively.

Finally, it is essential to emphasize that the studies mentioned above-included patients up to 2015, with consequent high use of BMS or old generation DES without new DAPT duration protocols.

In conclusion, "hard" evidence for DAPT in patients with liver cirrhosis is scarce. Based on retrospective studies (with older stents and protocols), PCI and DAPT appear to be safe but with a higher risk of bleeding complications with longer DAPT usage.

WHAT ARE POTENTIAL TOOLS THAT COULD BE USED TO ASSESS AND LOWER BLEEDING RISK?

Based on the aforementioned retrospective studies, PCI's usefulness in patients with liver cirrhosis regarding mortality is questionable due to high non-cardiovascular related mortality[36,37,39]. Therefore, appropriate triage of such patients before PCI, and consequent DAPT related bleeding risk, is mandatory. Based on data in the general population, PCI affects prognosis in patients presenting with MI and selected scenarios of a chronic coronary syndrome such as left main or proximal left anterior descending artery disease, a multi-vessel disease with impaired left ventricular systolic function, and a large area of myocardium at risk[6]. In our opinion, PCI is indicated in a patient with cirrhosis who presents with one of the mentioned scenarios if life expectancy, from the hepatological point of view, is reasonably long (one year) or other treatment modalities, such as LT are available. Except for the scenarios mentioned above, PCI of all significant coronary artery stenosis might be indicated before LT. This conclusion is based on retrospective studies that showed worse outcomes after LT in patients with CAD and increased mortality in multi-vessel CAD cases[40-42]. On the other hand, data from several studies indicate no impact of CAD on post-LT survival if CAD is treated appropriately, including PCI when indicated[43, 44]. All presented studies described CAD using plain angiography as the percentage of coronary artery stenosis (usually over 50%). Although this method is valid for CAD definition, more novel and precise methods, such as functional assessment of stenosis, should be done before PCI, especially in borderline stenosis and HBR patients[6]. Therefore, we advise the usage of instantaneous wave-free ratio or a similar method for confirmation of stenosis significance for all coronary artery stenosis estimated to be between 50%-90% as it not only affects prognosis but reduces the number of stents implanted compared to angiogram alone[6,45-47]. In the cases where PCI is indicated, it should be done with third generation DES, preferably with one tested for the short need for DAPT of only one month[6,33,34,48]. Another off-label option would be PCI using drug-coated balloons which has comparable results with modern DES primarily in small CAD (diameter ≤ 2.8 mm) and in HBR patients due to theoretical shorter usage of DAPT and lower risk for thrombosis as no foreign material remains in the artery[49-52]. We advise using the radial artery approach as default vascular access for all left heart catheterization due to better outcomes and lower bleeding risk than transfemoral access[6,53,54]. It also appears to be a safe option in patients with end-stage liver disease based on a single available study[55].

After the PCI, DAPT duration should be shortened in HBR patients, as advised by the guidelines, to three months after elective PCI or six months after PCI in acute coronary syndrome[56]. We also encourage clopidogrel usage compared to more potent P2Y12 inhibitors due to its lower bleeding risk[24,57,58]. A potential drawback of clopidogrel is that it requires activation in the liver[59]. However, a recent study

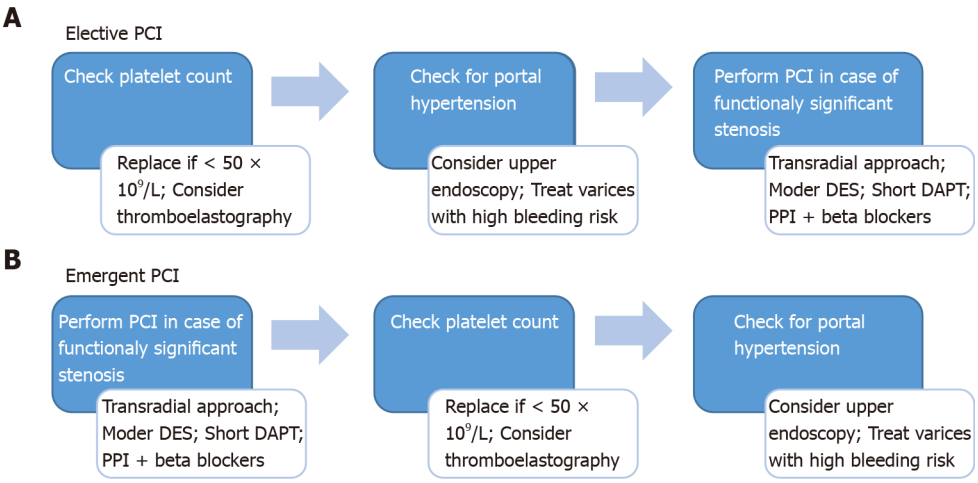

Figure 1 Proposed scheme with the main recommendations of how to approach a patient with cirrhosis undergoing percutaneous coronary intervention in elective and emergent settings. A and B: In case of elective percutaneous coronary intervention (PCI) (A), platelet count and portal hypertension work up should be performed (and treated) before the PCI. However, in emergent settings (B) above mentioned work up should be performed after the PCI. PCI: Percutaneous coronary intervention; DAPT: Dual antiplatelet therapy; DES: Drug eluting stent; PPI: Proton pump inhibitor.

described appropriately reduced platelet function after clopidogrel using thromboelastography (TEG), TEG-based platelet mapping, and impedance platelet aggregometry in patients with decompensated cirrhosis[60]. Importantly, no platelet function test has been studied for guiding DAPT in a patient with cirrhosis. On the other hand, TEG has been used to guide blood product use in various scenarios in patients with cirrhosis and impaired coagulation assessed using conventional methods (INR and platelet count)[61]. In randomized trials, TEG compared to conventional methods led to lower blood products use without an increase in bleeding complications in patients with bleeding varices and before invasive procedures[62,63]. Based on mentioned, TEG can theoretically be used to assess hemostatic pathways before administration of DAPT, with more freely DAPT usage in case of preserved hemostasis. However, these presumptions are supposed to be tested in clinical studies before widespread utilization.

Regarding medical therapy for preventing bleeding complications during DAPT, a proton pump inhibitor should be prescribed as it reduces upper gastrointestinal bleeding in patients with cirrhosis[36,64]. It is also most important to administer a maximally tolerated dose of beta-adrenergic blocking agents due to their positive effect on portal hypertension and CAD[28,65]. Lastly, we encourage repeat upper endoscopy in patients with liver cirrhosis before elective PCI or early after urgent PCI to manage varices according to recommendations for primary and secondary prophylaxis of variceal bleeding, as previously proposed[4,28].

In summary, PCI in patients with cirrhosis should be done over trans-radial artery access, using novel DES (with proved safety in short DAPT protocols), in cases when PCI is proved to affect patient prognosis. Along with DAPT, concomitant medical therapy that reduces the risk of bleeding should be administered. Novel approaches, such as TEG or "preventive" upper endoscopies, although promising, warn clinical conformation. Proposed scheme with the main recommendations of how to approach a patient with cirrhosis undergoing percutaneous coronary intervention in elective and emergent settings is presented in Figure 1.

CONCLUSION

The highest bleeding risk among patients with liver cirrhosis is present in a subgroup of patients with severe thrombocytopenia and elevated portal pressure. Therefore, every effort should be made to maintain thrombocyte count above > 50 × 10^9/L and prevent variceal bleeding. Despite the lack of solid evidence for DAPT in patients with cirrhosis, results from trials investigating shorter DAPT duration after PCI in HBR patient population can be implemented in patients with cirrhosis. Finally, novel methods in the assessment of CAD severity should be performed to avoid unnecessary PCI.

REFERENCES

1 **Kalaitzakis E**, Rosengren A, Skommevik T, Björnsson E. Coronary artery disease in patients with liver cirrhosis. *Dig Dis Sci* 2010; **55**: 467-475 [PMID: 19242795 DOI: 10.1007/s10620-009-0738-z]

2 **An J**, Shim JH, Kim SO, Lee D, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS. Prevalence and prediction of coronary artery disease in patients with liver cirrhosis: a registry-based matched case-control study. *Circulation* 2014; **130**: 1353-1362 [PMID: 25095888 DOI: 10.1161/CIRCULATIONAHA.114.009278]

3 **Raval Z**, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, Fix OK, Kay N, Abecassis MI, Gheorghiade M, Flaherty JD. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol* 2011; **58**: 223-231 [PMID: 21737011 DOI: 10.1016/j.jacc.2011.03.026]

4 **Russo MW**, Pierson J, Narang T, Montegudo A, Eskind L, Gulati S. Coronary artery stents and antiplatelet therapy in patients with cirrhosis. *J Clin Gastroenterol* 2012; **46**: 339-344 [PMID: 22105182 DOI: 10.1097/MCG.0b013e3182371258]

5 **Patel SS**, Nabi E, Guzman L, Abbate A, Bhati C, Stravitz RT, Reichman T, Matherly SC, Driscoll C, Lee H, Luketic VA, Sterling RK, Sanyal AJ, Patel V, Levy M, Siddiqui MS. Coronary artery disease in decompensated patients undergoing liver transplantation evaluation. *Liver Transpl* 2018; **24**: 333-342 [PMID: 29328556 DOI: 10.1002/lt.25012]

6 **Neumann FJ**, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; **40**: 87-165 [PMID: 30165437 DOI: 10.1093/eurheartj/ehy394]

7 **Singh V**, Patel NJ, Rodriguez AP, Shantha G, Arora S, Deshmukh A, Cohen MG, Grines C, De Marchena E, Badheka A, Ghatak A. Percutaneous Coronary Intervention in Patients With End-Stage Liver Disease. *Am J Cardiol* 2016; **117**: 1729-1734 [PMID: 27103158 DOI: 10.1016/j.amjcard.2016.03.010]

8 **Vetrovec G**, Stravitz RT. Bleeding in Patients With Cirrhosis Undergoing Invasive Cardiovascular Procedures: Do We Overestimate Risk? *Circulation* 2020; **141**: 1279-1281 [PMID: 32310692 DOI: 10.1161/CIRCULATIONAHA.120.043561]

9 **O'Leary JG**, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. *Gastroenterology* 2019; **157**: 34-43.e1 [PMID: 30986390 DOI: 10.1053/j.gastro.2019.03.070]

10 **Tsochatzis EA**, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014; **383**: 1749-1761 [PMID: 24480518 DOI: 10.1016/S0140-6736(14)60121-5]

11 **Tripodi A**. Hemostasis abnormalities in cirrhosis. *Curr Opin Hematol* 2015; **22**: 406-412 [PMID: 26203733 DOI: 10.1097/MOH.0000000000000164]

12 **Tripodi A**, Primignani M, Lemma L, Chantarangkul V, Mannucci PM. Evidence that low protein C contributes to the procoagulant imbalance in cirrhosis. *J Hepatol* 2013; **59**: 265-270 [PMID: 23583273 DOI: 10.1016/j.jhep.2013.03.036]

13 **Sinegre T**, Duron C, Lecompte T, Pereira B, Massoulier S, Lamblin G, Abergel A, Lebreton A. Increased factor VIII plays a significant role in plasma hypercoagulability phenotype of patients with cirrhosis. *J Thromb Haemost* 2018; **16**: 1132-1140 [PMID: 29577605 DOI: 10.1111/jth.14011]

14 **Qi X**, Ye C, Guo X. Recombinant factor VIIa for variceal bleeding in liver cirrhosis: still only a hope. *Arch Med Sci* 2017; **13**: 496-499 [PMID: 28261306 DOI: 10.5114/aoms.2017.65331]

15 **Bosch J**, Thabut D, Bendtsen F, D'Amico G, Albillos A, González Abraldes J, Fabricius S, Erhardtsen E, de Franchis R; European Study Group on rFVIIa in UGI Haemorrhage. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology* 2004; **127**: 1123-1130 [PMID: 15480990 DOI: 10.1053/j.gastro.2004.07.015]

16 **Tripodi A**, Chantarangkul V, Primignani M, Clerici M, Dell'era A, Aghemo A, Mannucci PM. Thrombin generation in plasma from patients with cirrhosis supplemented with normal plasma: considerations on the efficacy of treatment with fresh-frozen plasma. *Intern Emerg Med* 2012; **7**: 139-144 [PMID: 21298360 DOI: 10.1007/s11739-011-0528-4]

17 **Giannini EG**, Stravitz RT, Caldwell SH. Correction of hemostatic abnormalities and portal pressure variations in patients with cirrhosis. *Hepatology* 2014; **60**: 1442 [PMID: 24452495 DOI: 10.1002/hep.27029]

18 **Qamar AA**, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, Ripoll C, Maurer R, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Makuch R, Rendon G; Portal Hypertension Collaborative Group. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clin Gastroenterol Hepatol* 2009; **7**: 689-695 [PMID: 19281860 DOI: 10.1016/j.cgh.2009.02.021]

19 **Daly ME**. Determinants of platelet count in humans. *Haematologica* 2011; **96**: 10-13 [PMID: 21193429 DOI: 10.3324/haematol.2010.035287]

20 **Cesar JM**, Vecino AM. Survival and function of transfused platelets. Studies in two patients with congenital deficiencies of platelet membrane glycoproteins. *Platelets* 2009; **20**: 158-162 [PMID: 19437332 DOI: 10.1080/09537100902751925]

21 **Intagliata NM**, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F; faculty of the 7th International Coagulation in Liver Disease. Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease

Conference. *Thromb Haemost* 2018; **118**: 1491-1506 [PMID: 30060258 DOI: 10.1055/s-0038-1666861]

22 **Joist JH**. AICF and DIC in liver cirrhosis: expressions of a hypercoagulable state. *Am J Gastroenterol* 1999; **94**: 2801-2803 [PMID: 10520824 DOI: 10.1111/j.1572-0241.1999.02801.x]

23 **Giannini EG**, Greco A, Marenco S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. *Clin Gastroenterol Hepatol* 2010; **8**: 899-902; quiz e109 [PMID: 20601131 DOI: 10.1016/j.cgh.2010.06.018]

24 **McCarthy CP**, Steg G, Bhatt DL. The management of antiplatelet therapy in acute coronary syndrome patients with thrombocytopenia: a clinical conundrum. *Eur Heart J* 2017; **38**: 3488-3492 [PMID: 29020292 DOI: 10.1093/eurheartj/ehx531]

25 **Scharf RE**. Thrombocytopenia and Hemostatic Changes in Acute and Chronic Liver Disease: Pathophysiology, Clinical and Laboratory Features, and Management. *J Clin Med* 2021; **10** [PMID: 33917431 DOI: 10.3390/jcm10071530]

26 **Garcia-Tsao G**. Current Management of the Complications of Cirrhosis and Portal Hypertension: Variceal Hemorrhage, Ascites, and Spontaneous Bacterial Peritonitis. *Dig Dis* 2016; **34**: 382-386 [PMID: 27170392 DOI: 10.1159/000444551]

27 **Ripoll C**, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS, Bosch J; Portal Hypertension Collaborative Group. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007; **133**: 481-488 [PMID: 17681169 DOI: 10.1053/j.gastro.2007.05.024]

28 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018; **69**: 406-460 [PMID: 29653741 DOI: 10.1016/j.jhep.2018.03.024]

29 **Urban P**, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, Farb A, Gibson CM, Gregson J, Haude M, James SK, Kim HS, Kimura T, Konishi A, Laschinger J, Leon MB, Magee PFA, Mitsutake Y, Mylotte D, Pocock S, Price MJ, Rao SV, Spitzer E, Stockbridge N, Valgimigli M, Varenne O, Windhoevel U, Yeh RW, Krucoff MW, Morice MC. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. *Circulation* 2019; **140**: 240-261 [PMID: 31116032 DOI: 10.1161/CIRCULATIONAHA.119.040167]

30 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

31 **Child CG**, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964; **1**: 1-85 [PMID: 4950264]

32 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

33 **Urban P**, Meredith IT, Abizaid A, Pocock SJ, Carrié D, Naber C, Lipiecki J, Richardt G, Iñiguez A, Brunel P, Valdes-Chavarri M, Garot P, Talwar S, Berland J, Abdellaoui M, Eberli F, Oldroyd K, Zambahari R, Gregson J, Greene S, Stoll HP, Morice MC; LEADERS FREE Investigators. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. *N Engl J Med* 2015; **373**: 2038-2047 [PMID: 26466021 DOI: 10.1056/NEJMoa1503943]

34 **Windecker S**, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, Zaman A, Hudec M, Poliacikova P, Abdul Ghapar AKB, Selvaraj K, Petrov I, Mylotte D, Pinar E, Moreno R, Fabbiocchi F, Pasupati S, Kim HS, Aminian A, Tie C, Wlodarczak A, Hur SH, Marx SO, Jankovic I, Brar S, Bousquette L, Liu M, Stone GW; ONYX ONE Investigators. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. *N Engl J Med* 2020; **382**: 1208-1218 [PMID: 32050061 DOI: 10.1056/NEJMoa1910021]

35 **Wu VC**, Chen SW, Chou AH, Ting PC, Chang CH, Wu M, Hsieh MJ, Wang CY, Chang SH, Lin MS, Hung KC, Hsieh IC, Chu PH, Wu CS, Lin YS. Dual antiplatelet therapy in patients with cirrhosis and acute myocardial infarction - A 13-year nationwide cohort study. *PLoS One* 2019; **14**: e0223380 [PMID: 31581275 DOI: 10.1371/journal.pone.0223380]

36 **Krill T**, Brown G, Weideman RA, Cipher DJ, Spechler SJ, Brilakis E, Feagins LA. Patients with cirrhosis who have coronary artery disease treated with cardiac stents have high rates of gastrointestinal bleeding, but no increased mortality. *Aliment Pharmacol Ther* 2017; **46**: 183-192 [PMID: 28488370 DOI: 10.1111/apt.14121]

37 **Lu DY**, Saybolt MD, Kiss DH, Matthai WH, Forde KA, Giri J, Wilensky RL. One-Year Outcomes of Percutaneous Coronary Intervention in Patients with End-Stage Liver Disease. *Clin Med Insights Cardiol* 2020; **14**: 1179546820901491 [PMID: 32030068 DOI: 10.1177/1179546820901491]

38 **Azarbal B**, Poommipanit P, Arbit B, Hage A, Patel J, Kittleson M, Kar S, Kaldas FM, Busuttil RW. Feasibility and safety of percutaneous coronary intervention in patients with end-stage liver disease referred for liver transplantation. *Liver Transpl* 2011; **17**: 809-813 [PMID: 21425429 DOI: 10.1002/lt.22301]

39 **Marui A**, Kimura T, Tanaka S, Miwa S, Yamazaki K, Minakata K, Nakata T, Ikeda T, Furukawa Y, Kita T, Sakata R; CREDO-Kyoto Investigators. Coronary revascularization in patients with liver cirrhosis. *Ann Thorac Surg* 2011; **91**: 1393-1399 [PMID: 21396626 DOI: 10.1016/j.athoracsur.2011.01.022]

40 **Diedrich DA**, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant Proc* 2008; **40**: 3554-3557 [PMID: 19100436 DOI: 10.1016/j.transproceed.2008.08.129]

41 **Plotkin JS**, Scott VL, Pinna A, Dobsch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1996; **2**: 426-430 [PMID: 9346688 DOI: 10.1002/Lt.500020604]

42 **Yong CM**, Sharma M, Ochoa V, Abnousi F, Roberts J, Bass NM, Niemann CU, Shiboski S, Prasad M, Tavakol M, Ports TA, Gregoratos G, Yeghiazarians Y, Boyle AJ. Multivessel coronary artery disease predicts mortality, length of stay, and pressor requirements after liver transplantation. *Liver Transpl* 2010; **16**: 1242-1248 [PMID: 21031539 DOI: 10.1002/lt.22152]

43 **Satapathy SK**, Vanatta JM, Helmick RA, Flowers A, Kedia SK, Jiang Y, Ali B, Eason J, Nair SP, Ibebuogu UN. Outcome of Liver Transplant Recipients With Revascularized Coronary Artery Disease: A Comparative Analysis With and Without Cardiovascular Risk Factors. *Transplantation* 2017; **101**: 793-803 [PMID: 28099403 DOI: 10.1097/TP.0000000000001647]

44 **Wray C**, Scovotti JC, Tobis J, Niemann CU, Planinsic R, Walia A, Findlay J, Wagener G, Cywinski JB, Markovic D, Hughes C, Humar A, Olmos A, Sierra R, Busuttil R, Steadman RH. Liver transplantation outcome in patients with angiographically proven coronary artery disease: a multi-institutional study. *Am J Transplant* 2013; **13**: 184-191 [PMID: 23126562 DOI: 10.1111/j.1600-6143.2012.04293.x]

45 **Wolfrum M**, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, Fröhlich GM, Banning AP. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2016; **16**: 177 [PMID: 27608682 DOI: 10.1186/s12872-016-0355-7]

46 **Park SJ**, Ahn JM. Should we be using fractional flow reserve more routinely to select stable coronary patients for percutaneous coronary intervention? *Curr Opin Cardiol* 2012; **27**: 675-681 [PMID: 23044917 DOI: 10.1097/HCO.0b013e328358f587]

47 **Götberg M**, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Öhagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Tödt T, Venetsanos D, James SK, Kåregren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Fröbert O; iFR-SWEDEHEART Investigators. Instantaneous Wave-free Ratio *vs* Fractional Flow Reserve to Guide PCI. *N Engl J Med* 2017; **376**: 1813-1823 [PMID: 28317438 DOI: 10.1056/NEJMoa1616540]

48 **Ariotti S**, Adamo M, Costa F, Patialiakas A, Briguori C, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Ferlini M, Vranckx P, Valgimigli M; ZEUS Investigators. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention? *JACC Cardiovasc Interv* 2016; **9**: 426-436 [PMID: 26965932 DOI: 10.1016/j.jcin.2015.11.015]

49 **Latib A**, Colombo A, Castriota F, Micari A, Cremonesi A, De Felice F, Marchese A, Tespili M, Presbitero P, Sgueglia GA, Buffoli F, Tamburino C, Varbella F, Menozzi A. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. *J Am Coll Cardiol* 2012; **60**: 2473-2480 [PMID: 23158530 DOI: 10.1016/j.jacc.2012.09.020]

50 **Jeger RV**, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Leibundgut G, Weilenmann D, Wöhrle J, Richter S, Schreiber M, Mahfoud F, Linke A, Stephan FP, Mueller C, Rickenbacher P, Coslovsky M, Gilgen N, Osswald S, Kaiser C, Scheller B; BASKET-SMALL 2 Investigators. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet* 2018; **392**: 849-856 [PMID: 30170854 DOI: 10.1016/S0140-6736(18)31719-7]

51 **Liu W**, Zhang M, Chen G, Li Z, Wei F. Drug-Coated Balloon for De Novo Coronary Artery Lesions: A Systematic Review and Trial Sequential Meta-analysis of Randomized Controlled Trials. *Cardiovasc Ther* 2020; **2020**: 4158363 [PMID: 32934664 DOI: 10.1155/2020/4158363]

52 **Merinopoulos I**, Gunawardena T, Wickramarachchi U, Richardson P, Maart C, Sreekumar S, Sawh C, Wistow T, Sarev T, Ryding A, Gilbert T, Perperoglou A, Vassiliou VS, Eccleshall SC. Long-term safety of paclitaxel drug-coated balloon-only angioplasty for de novo coronary artery disease: the SPARTAN DCB study. *Clin Res Cardiol* 2021; **110**: 220-227 [PMID: 32876814 DOI: 10.1007/s00392-020-01734-6]

53 **Lee MS**, Wolfe M, Stone GW. Transradial *vs* transfemoral percutaneous coronary intervention in acute coronary syndromes: re-evaluation of the current body of evidence. *JACC Cardiovasc Interv* 2013; **6**: 1149-1152 [PMID: 24262614 DOI: 10.1016/j.jcin.2013.08.003]

54 **Valgimigli M**, Frigoli E, Leonardi S, Vranckx P, Rothenbühler M, Tebaldi M, Varbella F, Calabrò P, Garducci S, Rubartelli P, Briguori C, Andó G, Ferrario M, Limbruno U, Garbo R, Sganzerla P, Russo F, Nazzaro M, Lupi A, Cortese B, Ausiello A, Ierna S, Esposito G, Ferrante G, Santarelli A, Sardella G, de Cesare N, Tosi P, van 't Hof A, Omerovic E, Brugaletta S, Windecker S, Heg D, Jüni P; MATRIX Investigators. Radial *vs* femoral access and bivalirudin *vs* unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018; **392**: 835-848 [PMID: 30153988 DOI: 10.1016/S0140-6736(18)31714-8]

55 **Jacobs E**, Singh V, Damluji A, Shah NR, Warsch JL, Ghanta R, Martin P, Alfonso CE, Martinez CA, Moscucci M, Cohen MG. Safety of transradial cardiac catheterization in patients with end-stage liver

disease. *Catheter Cardiovasc Interv* 2014; **83**: 360-366 [PMID: 23723127 DOI: 10.1002/ccd.25043]

56 **Valgimigli M**, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018; **39**: 213-260 [PMID: 28886622 DOI: 10.1093/eurheartj/ehx419]

57 **Bhatt DL**, Hulot JS, Moliterno DJ, Harrington RA. Antiplatelet and anticoagulation therapy for acute coronary syndromes. *Circ Res* 2014; **114**: 1929-1943 [PMID: 24902976 DOI: 10.1161/CIRCRESAHA.114.302737]

58 **Bavishi C**, Panwar S, Messerli FH, Bangalore S. Meta-Analysis of Comparison of the Newer Oral P2Y12 Inhibitors (Prasugrel or Ticagrelor) to Clopidogrel in Patients With Non-ST-Elevation Acute Coronary Syndrome. *Am J Cardiol* 2015; **116**: 809-817 [PMID: 26119655 DOI: 10.1016/j.amjcard.2015.05.058]

59 **Jiang XL**, Samant S, Lesko LJ, Schmidt S. Clinical pharmacokinetics and pharmacodynamics of clopidogrel. *Clin Pharmacokinet* 2015; **54**: 147-166 [PMID: 25559342 DOI: 10.1007/s40262-014-0230-6]

60 **Trankle CR**, Vo C, Martin E, Puckett L, Siddiqui MS, Brophy DF, Stravitz T, Guzman LA. Clopidogrel Responsiveness in Patients With Decompensated Cirrhosis of the Liver Undergoing Pre-Transplant PCI. *JACC Cardiovasc Interv* 2020; **13**: 661-663 [PMID: 31883726 DOI: 10.1016/j.jcin.2019.08.038]

61 **Wei H**, Child LJ. Clinical utility of viscoelastic testing in chronic liver disease: A systematic review. *World J Hepatol* 2020; **12**: 1115-1127 [PMID: 33312434 DOI: 10.4254/wjh.v12.i11.1115]

62 **Rout G**, Shalimar, Gunjan D, Mahapatra SJ, Kedia S, Garg PK, Nayak B. Thromboelastography-guided blood product transfusion in cirrhosis patients with variceal bleeding: a randomized controlled trial. *J Clin Gastroenterol* 2020; **54**: 255-262 [PMID: 31008867 DOI: 10.1097/MCG.0000000000001214]

63 **De Pietri L**, Bianchini M, Montalti R, De Maria N, Di Maira T, Begliomini B, Gerunda GE, di Benedetto F, Garcia-Tsao G, Villa E. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. *Hepatology* 2016; **63**: 566-573 [PMID: 26340411 DOI: 10.1002/hep.28148]

64 **Khan SU**, Lone AN, Asad ZUA, Rahman H, Khan MS, Saleem MA, Arshad A, Nawaz N, Sattur S, Kaluski E. Meta-Analysis of Efficacy and Safety of Proton Pump Inhibitors with Dual Antiplatelet Therapy for Coronary Artery Disease. *Cardiovasc Revasc Med* 2019; **20**: 1125-1133 [PMID: 30773427 DOI: 10.1016/j.carrev.2019.02.002]

65 **Verma S**, Peterson EL, Liu B, Sabbah HN, Williams LK, Lanfear DE. Effectiveness of beta blockers in patients with and without a history of myocardial infarction. *Eur J Clin Pharmacol* 2020; **76**: 1161-1168 [PMID: 32440720 DOI: 10.1007/s00228-020-02886-0]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 November 26; 13(11): 608-627

DOI: 10.4330/wjc.v13.i11.608

ISSN 1949-8462 (online)

REVIEW

Cardiac monitoring for patients with palpitations

Jaume Francisco-Pascual, Javier Cantalapiedra-Romero, Jordi Pérez-Rodon, Begoña Benito, Alba Santos-Ortega, Jenson Maldonado, Ignacio Ferreira-Gonzalez, Nuria Rivas-Gándara

ORCID number: Jaume Francisco-Pascual 0000-0002-8841-2581; Javier Cantalapiedra-Romero 0000-0002-7032-9720; Jordi Pérez-Rodon 0000-0003-2234-5248; Begoña Benito 0000-0002-8668-1251; Alba Santos-Ortega 0000-0002-6286-0968; Jenson Maldonado 0000-0002-7986-7162; Ignacio Ferreira-Gonzalez 0000-0002-1208-5561; Nuria Rivas-Gándara 0000-0002-2101-8678.

Author contributions: Francisco-Pascual J prepared the concept, design, draft and editing of the manuscript; Cantalapiedra-Romero J contributed to collecting data, creating the tables and figures and writing part of the manuscript; all other authors contributed to the design and review of the manuscript and agreed with the content of its final version.

Conflict-of-interest statement: The Arrhythmia Unit receives fellowship grants from Boston Scientific and research grants from Abbott. J. Francisco-Pascual receives advisory and speaking honoraria from Abbott and Microport. N. Rivas-Gándara receives advisory and speaking honoraria from Abbott., B. Benito, J. Perez-Rodon and A. Santos-Ortega receives speaking honoraria from Abbott. The other authors report no conflicts.

Country/Territory of origin: Spain

Jaume Francisco-Pascual, Javier Cantalapiedra-Romero, Jordi Pérez-Rodon, Begoña Benito, Alba Santos-Ortega, Jenson Maldonado, Ignacio Ferreira-Gonzalez, Nuria Rivas-Gándara, Unitat d'Arritmies, Servei de Cardiologia, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona 08035, Spain

Jaume Francisco-Pascual, Jordi Pérez-Rodon, Begoña Benito, Alba Santos-Ortega, Ignacio Ferreira-Gonzalez, Nuria Rivas-Gándara, Facultat de Medicina, Universitat Autònoma de Barcelona, Bellaterra 08193, Barcelona, Spain

Jaume Francisco-Pascual, Jordi Pérez-Rodon, Begoña Benito, Alba Santos-Ortega, Ignacio Ferreira-Gonzalez, Nuria Rivas-Gándara, CIBER de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid 28029, Spain

Corresponding author: Jaume Francisco-Pascual, MD, Doctor, Senior Researcher, Staff Physician, Unitat d'Arritmies, Servei de Cardiologia, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Passeig Vall d'Hebron 119-129, Barcelona 08035, Spain. jafranci@vhebron.net

Abstract

Palpitations are one of the most common reasons for medical consultation. They tend to worry patients and can affect their quality of life. They are often a symptom associated with cardiac rhythm disorders, although there are other etiologies. For diagnosis, it is essential to be able to reliably correlate the symptoms with an electrocardiographic record allowing the identification or ruling out of a possible rhythm disorder. However, reaching a diagnosis is not always simple, given that they tend to be transitory symptoms and the patient is frequently asymptomatic at the time of assessment. In recent years, electrocardiographic monitoring systems have incorporated many technical improvements that solve several of the 24-h Holter monitor limitations. The objective of this review is to provide an update on the different monitoring methods currently available, remarking their indications and limitations, to help healthcare professionals to appropriately select and use them in the work-up of patients with palpitations.

Key Words: Palpitation; Cardiac monitoring; Electrocardiogram; Loop recorder

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 2, 2021
Peer-review started: May 2, 2021
First decision: June 17, 2021
Revised: June 27, 2021
Accepted: October 31, 2021
Article in press: October 31, 2021
Published online: November 26, 2021

P-Reviewer: Li X, Li A
S-Editor: Fan JR
L-Editor: Kerr C
P-Editor: Fan JR

Core Tip: In recent years, electrocardiographic monitoring systems have incorporated many technical improvements that solve several of the 24-h Holter monitor limitations. This review provides an update on the different electrocardiographic cardiac monitoring methods currently available, remarking their indications and limitations, to help healthcare professionals appropriately select and use them in the work-up of patients with palpitations.

Citation: Francisco-Pascual J, Cantalapiedra-Romero J, Pérez-Rodon J, Benito B, Santos-Ortega A, Maldonado J, Ferreira-Gonzalez I, Rivas-Gándara N. Cardiac monitoring for patients with palpitations. *World J Cardiol* 2021; 13(11): 608-627
URL: https://www.wjgnet.com/1949-8462/full/v13/i11/608.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i11.608

INTRODUCTION

Palpitations are one of the most common reasons for medical consultation and can occur in up to 10% of the population at some point in their lives[1-3]. They tend to worry patients and can affect their quality of life. They are a symptom that is frequently associated with cardiac rhythm disorders, although there are other etiologies[4] (Table 1). In fact, in up to half of the cases, palpitations are not due to a significative arrhythmia[2].

Having an accurate diagnosis is important to determinate the prognosis, to guide treatment and to plan the patient's follow-up. In order to have a diagnosis, it is essential to be able to reliably correlate the symptoms with an electrocardiographic record allowing the identification or ruling out of a possible rhythm disorder. However, reaching a diagnosis is not always simple, given that they tend to be transitory symptoms and the patient is asymptomatic at the time of assessment[1,5].

Electrocardiographic monitoring systems are a first-line tool in assessing these patients. The introduction of the 24-h Holter monitor within 60 s was a true revolution and its use rapidly became widespread[6]. Other than diagnosing palpitations, it has also been an important tool in understanding the physiological cardiac rhythm behavior[7,8] and in the follow-up of patients at risk of cardiovascular disease[8], in syncope work-up[9-12], in risk stratification of certain patients[13-16] or in the detection of silent arrhythmias[8,17-21]. Due to its high availability and probably due to a certain degree of tradition, it is the monitoring system most commonly used by most doctors. However, it has several limitations that reduce its efficiency and diagnostic yield[2,22].

Fortunately, in recent years, in line with the overall technological development that our society has experienced, electrocardiographic monitoring systems have incorporated many technical upgrades allowing for improvement in several of the limitations presented by the 24-h Holter monitor. This evolution of electrocardiogram (ECG) recording systems has occurred in various directions. On the one hand, we have the improvement in the quality and quantity of recordings, such that, at the present time, it is possible to obtain 12-lead ECG traces of excellent quality with increased monitoring time, be it in the form of a continuous recording (which can last up to a month), or in the form of intermittent recordings which can last up to 3 years in the case of implantable recorders[8,23-25]. On the other hand, various recording and analysis algorithms have been developed, which allow for many improvements; for example, the automatic analysis of arrhythmias[18,23]. Remote data transmission systems have also been incorporated with multiple designs able to adapt to each patient's different needs[8,24,26].

Unfortunately, these new devices are still not universally incorporated into daily clinical practice, either because they are not included or reimbursed in the healthcare systems, or due to the inertia of healthcare professionals[27]. In the work-up for palpitations, it is still usual to apply a traditional strategy that is fundamentally based on the use of a 24-h Holter monitor, which has low diagnostic yield on many occasions[2,22]. This lack of yield is due to the fact that the majority of the events to be diagnosed are paroxysmal ones that occur occasionally and unexpectedly. The use of standardized diagnostic protocols with the application of new electrocardiographic monitoring devices has been shown not only to markedly improve the diagnostic yield, but also to

Table 1 Principal cardiac and noncardiac causes of palpitations

	Cardiac and noncardiac causes
Cardiac arrhythmias	Premature contractions (supraventricular or ventricular)
	Supraventricular tachycardia (AF, flutter, AVRNT, *etc.*)
	Ventricular tachycardia
	Severe bradyarrhythmia/AV block
	Pacemaker mediated tachycardia
Structural heart disease	Severe aortic regurgitation
	Hypertrophic cardiomyopathy
	Congenital heart disease with significant shunt
	Mechanical prosthetic valves
Systemic causes	Thyroid dysfunction
	Pheochromocytoma
	Anaemia
	Fever
	Hypoglycaemia
	Arteriovenous fistula
	Autonomic dysfunction
Psychosomatic disorders	Anxiety
	Somatisation disorder
Drugs	Sympathomimetic agents (bronchodilators, antidepressants)
	Vasodilators (hydralazine, doxazosin)
	Recreational: Cocaine, alcohol, amphetamines, cannabis

AVRNT: Atrioventricular nodal re-entry tachycardia; AF: Atrial fibrillation; AV: Atrioventricular.

be clearly cost efficient[2,28-30].

However, it should also be noted that the new devices are not exempt from limitations. Some are related to patient tolerance, either due to the possibility of relative discomfort, the need to wear external devices with electrodes stuck to the skin, or because the implantable devices require a minor surgical procedure, meaning that certain patients may not accept them[8,24,27]. Also, the devices continue to record a significant number of artifacts or rhythmic abnormalities that are not pathological or significant, which inefficiently lengthen the interpretation time of the studies and can even saturate the memory of certain devices. In addition, it should be noted that for a suitable diagnosis to be made, not only is it important to have recorded a quality electrocardiographic trace; the latter must also be properly interpreted in the patient's clinical context, which requires sufficient skill on the part of the healthcare professional interpreting the trace[31].

The objective of this review is to offer an update on the different monitoring methods currently available, their indications and limitations, to help healthcare professionals appropriately select and use them in the work-up of patients with palpitations.

ELECTROCARDOGRAPHIC CARDIAC MONITORING DEVICES

Device classification

The monitoring devices available on the market have differing characteristics. Traditionally, these devices have been classified into three or four groups [24/48-h Holter, external prospective event recorders (PERs), loop recorders (LRs)] based on a series of shared characteristics[8,27] (Table 2). However, thanks to technical develop-

Table 2 Main advantages, limitations, and indications of the most commonly used models of cardiac monitoring devices

	Advantages	Disadvantages	Main indications
24 h Holter	Continuous recording	Discomfort for the patient	Very frequent (daily) symptoms
	12 leads with good correlation with surface ECG	Artefacts	Permanent AF rate monitoring
	Low economic cost	Maximum recording of 24-48 h (low diagnostic yield)	Frequent ventricular premature beats
			Risk stratification of (hypertrophic) cardiomyopathies
Skin patches	Continuous recording of 7–14 d	Single use and greater economic cost	Frequent (weekly) symptoms
	Good tolerability for patients	Analysis by external companies	AF detection in cryptogenic stroke (2 wk)
		Only one lead[1]	
External loop recorders	Loop recording (includes beginning and end of arrhythmic event)	Patient discomfort	Occasional symptoms (monthly)
	4 wk monitoring	Requires education from healthcare professional on how to correctly place the electrodes	AF detection in cryptogenic stroke (2–4 wk)
	High yield and efficiency in the assessment of palpitations		
Implantable loop recorder	Loop recording	Invasiveness and associated complications (infection, bleeding, *etc.*)	Very infrequent symptoms
	Up to 3-yr monitoring (good diagnostic yield)	Individual economic cost	AF detection in at-risk patients (cryptogenic stroke, post-ablation, *etc.*)
	Patient does not have to do anything	Single lead	Syncope
	Remote monitoring		
External event recorders/mobile devices	Easy access for the general population	Single lead[1]	Palpitations work-up
	Possibility of prolonged use (years)	Data management	Population AF screening (not validated)
	Screening for asymptomatic events (AF screening)	Patient has to be involved (not suitable for syncope work-up)	
	Remote monitoring		

[1]There are devices with more leads.

AF: Atrial fibrillation; ECG: Electrocardiogram.

ments in recent years, the devices have gained in functionality and taken on new properties, making it difficult to establish a strict, closed classification. For this reason, some devices will have mixed characteristics between two groups (or will be able to be used in one or other manner according to the patient). Despite this, we should mention some of the most differentiating characteristics allowing a device and specific model to be classified (Figure 1). These characteristics must be considered when indicating the device that best suits each patient.

They may, thus, be classified according to the following.

(1) Monitoring time. There are short recording devices (24–48 h) that are useful for the examination of symptoms that occur every day or frequently; mid-range recording devices (up to 4 wk) and long recording devices (up to 3–4 years)[32]. Due to limitations of data storage, when we increase the monitoring time of the devices, they switch from continuous to intermittent recording, as will be discussed later. To achieve appropriate diagnostic yield in the work-up for palpitations, it is essential to adjust the monitoring time to the frequency of the symptoms. This is, without a doubt, one of the main characteristics when selecting a device.

(2) Recording type. This is another important characteristic to be kept in mind when selecting the most suitable test for each patient type. On the one hand, continuous recording devices such as Holter monitors make a constant ECG recording that can

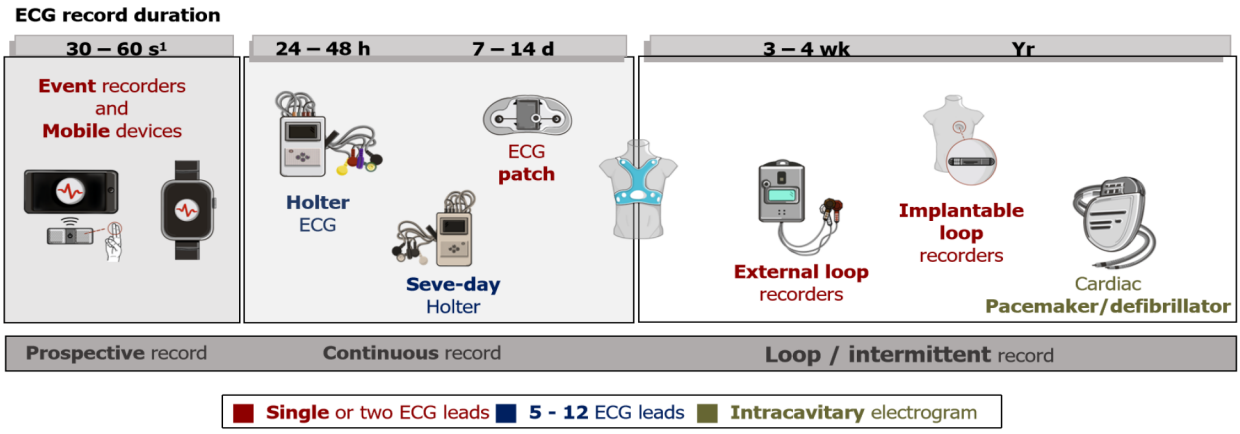

Figure 1 Main electrocardiographic monitoring devices available according to electrocardiogram recording duration and type and number of derivations. [1]While they prospectively register 30–60 s, they may be used repeatedly on a long-term basis. ECG: Electrocardiogram.

later be reviewed in its entirety. Continuous recordings avoid information loss since they do not depend on activation by the patient or on arrhythmia detection algorithms. By contrast, tests using intermittent recording are patient-activated or activate automatically according to different arrhythmia detection algorithms. There are two distinct types of device with this characteristic: Loop recorders [external LRs (ELRs) or implantable LRs (ILRs)] and PERs. The main difference between them is the ability of the LR to record the trace both prospectively and retrospectively, allowing us to obtain the trace from the start of the event (which may be important for the precise diagnosis of certain arrhythmias) (Figure 2). Similarly, LRs have various algorithms allowing for the automatic recording of certain asymptomatic arrhythmias, which prospective recorders do not allow for, since they are only activated by the patient in the event of symptoms (as such, they are also not useful for syncope work-up)[17,32,33]. It should be noted that there are currently certain devices available with continuous recording capacity as well as off-line analysis software with detection algorithms for arrhythmias that present the information in a similar manner to event recorders (although the healthcare professional can review the rest of the recording if this is considered important)[19,34,35].

(3) Number of leads. Recordings range from systems with just one lead to full 12-lead ECGs in the devices with the most leads. It is important to keep in mind that, the greater the number of leads, the more memory the device will use. In addition, there will be a greater number of electrodes to be applied by the patient in order for the recording to be made. As such, as a general rule, the devices allowing for long monitoring times offer a limited number of leads. However, having more than one lead is often useful. For example, on occasion, it allows for the clearing up of doubts as to whether a lead is subject to artifacts (Figure 3) or to better assess the wave morphology, which is important on certain occasions[8,36,37].

(4) Degree of invasiveness. There are implantable and external devices. ILRs require a minor surgical procedure, but once the wound has healed, patients do not usually notice them, and they allow for prolonged monitoring[17,25].

(5) Connectivity. The most up-to-date devices incorporate connectivity systems that allow for remote monitoring. Some can even be linked to smartphones, allowing for the easy sharing and sending of recordings *via* the Internet or Bluetooth[26,32,38,39]. In addition, some applications have algorithms that offer the patient an instantaneous diagnosis of their arrhythmia (although it is recommended that this is ratified by a healthcare professional)[18,40,41].

(6) Automatic algorithms. Different recording and analysis algorithms have been developed in recent years and they have been incorporated into some devices. Most of these algorithms allow for the automatic analysis of arrhythmias such as atrial fibrillation (AF), bradycardia, or asystole, but some of them also allow for the filtering out of noise to try to improve recording quality. There are differences between the algorithms that different brands incorporate into their devices. It is important to evaluate not only the algorithms that they provide, but also their sensitivity and specificity for detecting each type of arrhythmia. All of them should have type I and type II errors, but there may be significant differences depending on the device. Therefore, when selecting a monitoring device, physicians should also consider the accuracy of these algorithms.

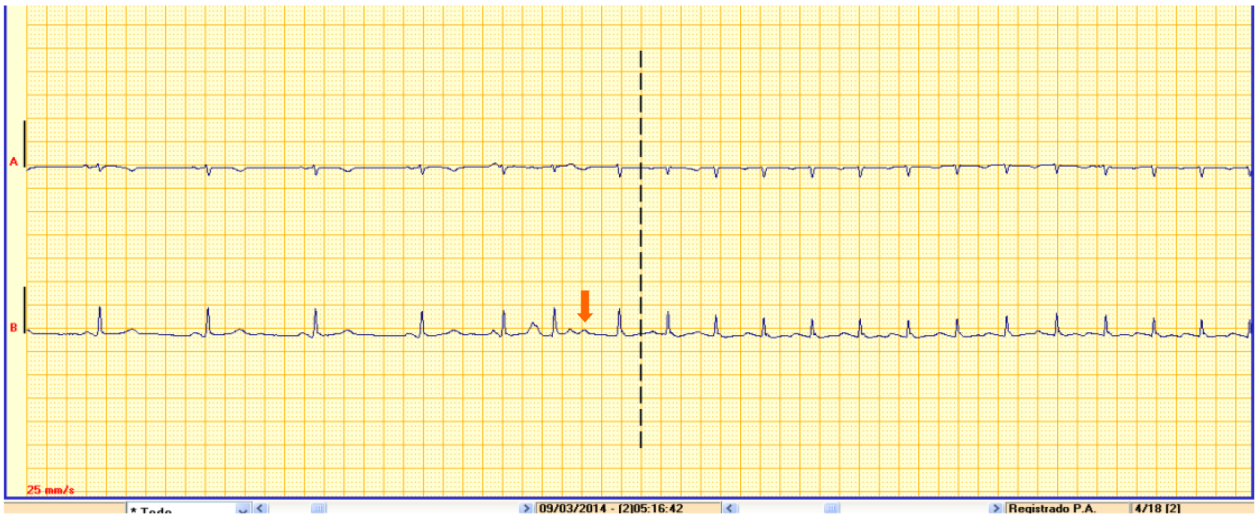

Figure 2 Example of an electrocardiogram trace obtained with an external loop recorders in a patient with palpitations. The beginning of a supraventricular tachycardia (SVT) is observed. A premature atrial beat that conducts with long PR seems to be the trigger of the SVT. This finding is highly suggestive of atrioventricular nodal re-entry tachycardia.

(7) Recording system type used. Initially, most devices used adhesives with electrodes. This is still the most common used format, although others have been developed that can record the cardiac signal, such as patches, belts or vests[8,24]. There are also devices that do not need to be in constant contact with the patient which incorporate electrodes into the recorder's own case, which are brought close to the skin when a recording is desired[42-44].

(8) Availability of other biological signals. In addition to recording the electrocardiographic trace, some devices have sensors that allow other biological signals to be monitored, such as physical activity, bodily position, oxygen saturation and even the presence of apnea[39,45,46].

Main electrocardiographic monitoring devices available

As noted above, there is currently a wide variety of monitoring devices offering a combination of characteristics, which makes it difficult to perform a strict classification. However, it is still useful to differentiate certain major groups (Figure 1 and Table 2), in the knowledge that certain models may have mixed characteristics between two groups or may be used in different ways as appropriate *(e.g.,* there are devices that can function as a 24-h Holter monitor, a continuous 3-wk Holter or a loop recorder) .

Continuous Holter (24/48-h): This takes its name from the cardiologist Norman J. Holter, who developed this technology in 1961. It is currently the most common technique used in clinical practice[47]. Currently, most Holter devices consist of a lightweight recorder with a digital memory card and a series of cutaneous electrodes that obtain a continuous ECG recording. They allow for 24-48-h monitoring time in most cases, although there are devices with recording capacities of up to 7 d.

Originally, the recording was made up of only two or three leads and, still today, many tests are carried out in this way. However, as early as 1966, the first 12-lead Holter monitor was developed with a system of 10 electrodes arranged over the patient's torso. Later on, a simplified five-electrode system was developed (the EASI system) which allowed for the reconstruction of 12 leads with good clinical reliability [48]. Having 12 leads may be especially important when assessing certain arrhythmias, such as the morphology of ventricular extrasystoles or certain repolarization patterns which may only appear in one specific lead. Torso electrodes avoid possible artifacts and discomfort associated with the positioning of the electrodes on the limbs. However, it should be noted that this arrangement attenuates the amplitude of the inferior leads and generates a slight right cardiac axis deviation[48], and some recordings obtained with torso leads cannot be considered completely equivalent to standard ECG leads[8].

After completing the recording, it is transferred into software installed on a computer (and/or a server in the cloud in some of the more advanced devices), which usually allows for an initial automatic analysis identifying the QRS complexes and the

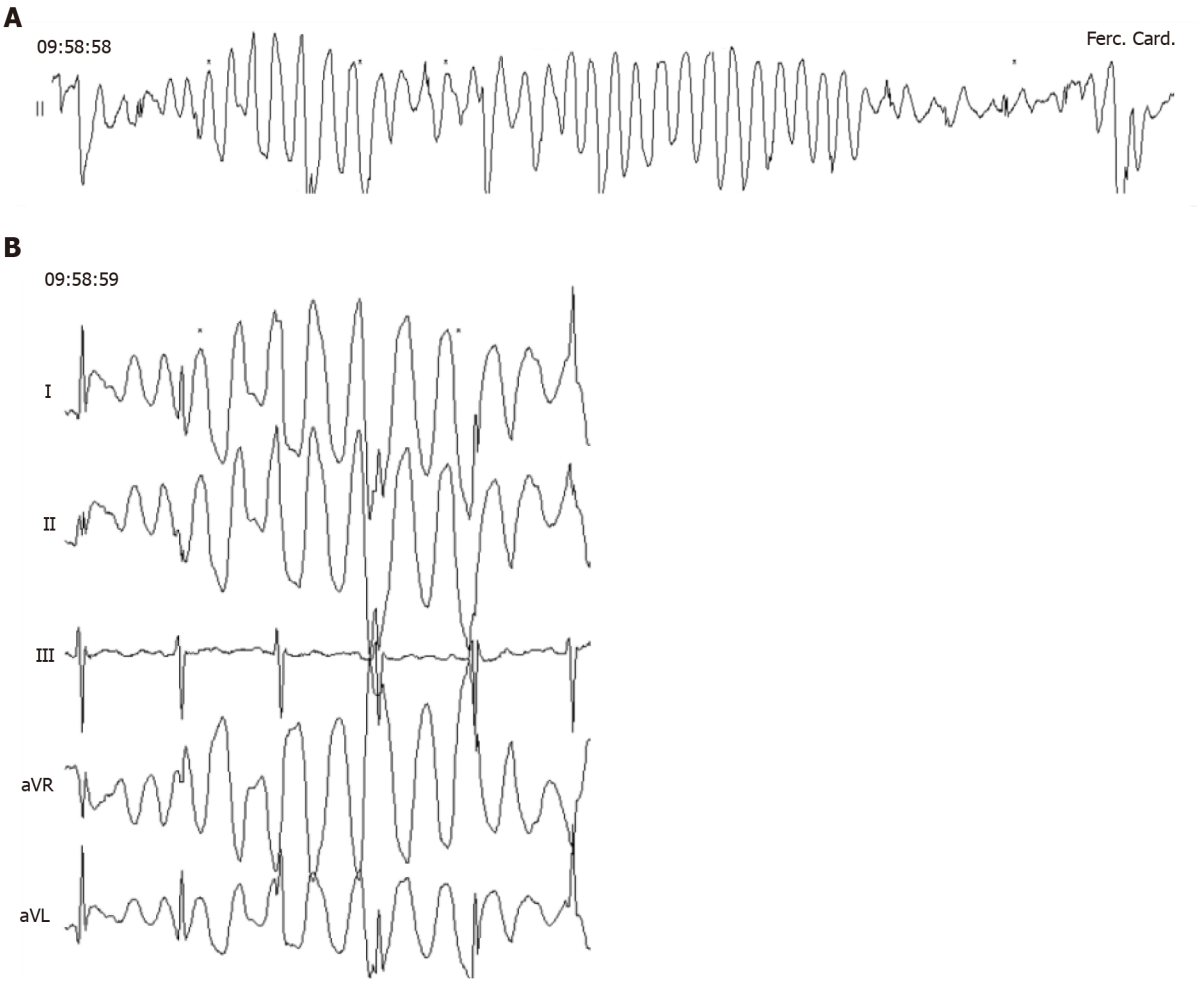

Figure 3 Example of an electrocardiogram tracing obtained with a Holter monitor with single-lead or multiple leads. A: A polymorphic trace is apparent with a single-lead record; B: After checking the other leads, the artifact can be easily identified.

R-R interval to offer values such as maximum/minimum rate, histograms of rate or ST segment analysis. Finally, the healthcare professional must review the data to rule out the presence of possible artifacts and interpret the results of the ECG taking into account the patient's symptom diary[47].

Holter monitors have demonstrated their utility in identifying arrhythmias in patients with palpitations or syncope with different efficacy values in line with the pretest probability of the population studied and the frequency of the symptoms[2,22,28]. In recent years, various case series, including our own[2,32], have shown that the global diagnostic yield of Holter monitors is limited and that, despite the fact that its cost is generally relatively low, its per-diagnosis cost is high[22,27,47]. For example, in a transversal study in usual clinical practice carried out by our group, Holter only offered a diagnostic yield of 3.5% for syncope and 16.5% for palpitations. This yield is even lower when the objective is screening for asymptomatic arrhythmias, such as AF in the context of cryptogenic stroke, where the yield can be < 1%[32].

Among other indications that have been considered, there was risk stratification in certain groups of patients, either through the detection of nonsustained arrhythmias and abnormalities of heart rate variability parameters or dispersion of the QT interval [15,49-53]. However, at the present time, few therapeutic decisions are based on Holter findings, perhaps with the exception of the presence of nonsustained ventricular tachycardia in patients with hypertrophic cardiomyopathy[15], which may be a decisive factor for the implantation of an implantable cardiac defibrillator.

In our opinion, in the work-up for palpitations at the present time, the 24/48-h Holter monitor should only be considered in patients with daily or very frequent symptoms. When this is not the case, there are other tools available that offer not only a greater diagnostic yield, but also better cost efficiency[2,39,54].

Skin patches: These systems, which were developed over the past decade, enjoy a certain degree of popularity in some countries. However, in others, such as Spain, their

use remains marginal. They consist of patches of different materials, which adhere to the skin and contain electrodes to obtain one (the most common) or two ECG leads for 7–14 d' monitoring. The device itself acquires, amplifies and filters the ECG signal, which is then telematically transmitted for analysis (usually through an external company)[8,24,55].

There are different patch models with different recording characteristics. In some cases, they are similar to a Holter monitor and in others to an ELR. For example, the ZioPatch creates a continuous ECG recording with a single lead that is interpreted *via* an analysis platform. It also has a symptom button on the patch itself[56,57]. Another different example is the NUVANT-Piix. It also has only one lead, but it does not perform a continuous recording; rather, it only records the traces identified as arrhythmias or when the patient experiences symptoms and activates the device with a special magnet[58].

There are studies comparing the efficacy of these new patches with traditional Holter monitors (Table 3), showing good tolerability on the part of patients and a greater diagnostic yield, particularly for the purposes of identifying paroxysmal AF [56,59]. However, these devices have a higher cost and are usually single use[8,56].

In this section, we can also include the so-called "textrodes", which are electrodes included in garments[34]. These devices are currently in a more experimental phase. One of the main problems they entail is the quantity of artifacts due to movement of the fabric. In this regard, studies are being carried out to select the best material and electrode positioning within the fabric[60,61].

Prospective external event recorders (without loop memory) and mobile devices: These tend to be small devices with a couple of electrodes incorporated into them, which allow, when activated by the patient, for a real-time recording of 30–60 s of a single ECG lead[8,24,41,44]. These devices allow for the recording of episodes of palpitations that are sufficiently long for the patient to have time to apply the recorder. However, they have the limitation of not allowing for the recording of the start of the episodes, which is frequently important for diagnosis when it comes to interpreting the mechanism of arrhythmias[32,39] (Figure 2). Similarly, their use is not appropriate for syncope work-up, because if the patient applies the device having recovered from the syncopal episode, in most cases, the possible cause of the syncope will have disappeared[10].

In recent years, these devices have become popular, since they are small devices that do not have to be constantly in contact with the patient and allow for prolonged use (even years, since the batteries can be recharged and they only record when activated), as well as having a relatively low cost. There are currently numerous models from different brands, with various designs. In addition, some of these models link to or are even included as tools belonging to smartphones or smartwatches (such as the Apple Watch), which allows for greater and easier access for the general public[24,40]. Indeed, a significant number of users, especially those of smartwatches, have no medical indication, which may also be controversial[62].

In most models, the recordings are stored in the device itself or in a linked mobile phone. Many incorporate their own algorithms which allow for the identification of certain types of arrhythmia (especially AF), and offer the option of being sent to health centers for interpretation[40,41,44].

Due to their simple use and accessibility, these applications' utility for other indications such as population AF screening (most useful in patients aged > 65 years) [63,64] or also for the detection of cardiac ischemia has been analyzed[65-67], which could facilitate diagnosis in patients who live far away from health centers. New mobile devices are also being developed (they are not yet on the market) which obtain an ECG signal from the patient on an involuntary basis while the devices are being used as normal, which would allow for the intermittent detection of asymptomatic cardiac rhythm disorders[44,63,64,68].

LRs: These allow for more prolonged monitoring, since they do not store a continuous recording[2,49,69]. Even though they continuously monitor the ECG, the device only stores it in its memory for a few minutes before subsequently overwriting it with a newer recording (initially it was an endless circular tape, although the devices are now digital). Only when the device is activated (either *via* manual activation or an automatic arrhythmia detection algorithm), it records on another part of the memory (where it will not be deleted and can be reviewed) the recording from a few minutes before the start of the event until its end. In this way, since several minutes before activation are stored in the device memory, the likelihood of recording the trace at the time of the syncope episode (if it is activated for syncope), or the start of the episode of

Table 3 Summary of relevant studies on diagnostic yield for palpitations according to the different types of devices

Ref.	No. of patients	Study design	Study population	Duration of monitoring	Diagnostic yield	Other findings
Holter 24 h						
Sulfi *et al*[22], 2008	2688	Retrospective cohort	Palpitations and basal sinus rhythm	24 h	16%	Even less diagnostic yield in patients aged < 50 yr
Paudel *et al* [103], 2013	335	Single-center prospective cohort	Palpitations	24 h	75%	40% of patients with ventricular ectopy considered as diagnostic finding (possible selection bias)
ECG patchs						
Barrett *et al*[59], 2014	146	Prospective cohort comparing Patch *vs* 24 h Holter	Palpitations	15 d	60% more diagnostics than 24 h Holter	Over 90% of patients were comfortable with it. Best diagnostic yield during first week
Event recorders						
Narasimha *et al* [104], 2018	38	Prospective cohort comparing Kardia Mobile *vs* ELR (simultaneously)	Palpitations (less often than daily but more than monthly)	14–30 d	89.5% *vs* 68% in ELR group	Better compliance with Kardia Mobile
Hall *et al*[63], 2020	11 studies (> 20000 patients)	Systematic review	AF screening in general population	Heterogeneous	Up to 36% (depending of population's AF burden)	More diagnostic yield in people aged > 65 yr. Approximately 4% of uninterruptable registries
ELR						
Locati *et al*[54], 2016	392 (282 with palpitations)	Prospective cohort	> 2 episodes in last year	4 wk	71.6%	Early recorder use increase diagnostic yield. Diagnostic yield for syncope: 24.5%
Francisco-Pascual *et al*[2], 2019	149 (91 in ELR group)	Prospective ELR cohort compared with historical Holter cohort	> 2 episodes in last year	21 d	86.8%	Holter diagnostic yield: 20.7%. ELR reduce the cost *per* diagnosis
ILR						
Giada *et al*[29], 2007	50 (26 in ILR group)	Prospective cohort comparing ILR with conventional strategy	1 episode *per* month or less (longer than 1 min)	321 d (mean)	73%	Mean time to diagnosis: 279 d. Lower cost *per* diagnosis in ILR group
Padmanabhan *et al*[83], 2019	312 (51 with palpitations)	Prospective cohort of consecutive patients with an ILR implanted	Any indication form monitoring (16.3% due to palpitations)	579 d (mean)	64.7%	38.7% useful in ruling out an arrhythmic cause for symptoms (all indications). 12% AF.

ELR: External loop recorders; AF: Atrial fibrillation; ILR: Implantable loop recorders.

palpitations, is high[2,54,70,71].

At the present time, most LRs can record symptomatic arrhythmias after activation by the patient, usually in the context of symptoms, or silent arrhythmias on an automatic basis[25]. Within this category, we differentiated between external and implantable devices.

(1) ELRs: External event recorders are characterized by a loop memory, which uses cutaneous electrodes to record, be this in the form of independent electrodes or those integrated into a t-shirt. The patients themselves position the electrodes daily[8,25].

Due to the characteristics of these devices, these systems tend to be worn by patients for no more than a few weeks (usually 3–4 wk, although there are reports of more prolonged periods). They are useful for the investigation of symptoms that occur every 2 or 3 wk. It should be noted that palpitations usually occur more frequently than syncopal episodes, hence the diagnostic yield for palpitations is approximately 80% [2], whereas in cases where it is indicated for syncope, it is no greater than 10%[54,72-74] (Table 3).

The quality of the recordings tends to be good, although there may be a not insignificant number of recordings corresponding to an artifact. Another limitation may be patient adherence to the daily positioning of the electrodes, even though this is

generally good, as well as the possibility that the patient may develop an allergy to the electrodes, even though this is rare[54,72].

In the investigation of palpitations, in addition to a high diagnostic yield, it allows for improved cost efficiency in the work-up of these patients[2,73]. A recent study by our group[2] compared the use of ELRs with a conventional Holter strategy in patients with more than two episodes of palpitations *per* year. We were able to demonstrate that investigation in the form of a diagnostic protocol, including that the use of an ELR, had a notably superior diagnostic yield (86% *vs* 21%) and offered a significant reduction in per-diagnosis cost (€375.13 in the ELR group and €5184.75 in the control group ($P < 0.001$). The cost-effectiveness study revealed that the systematic use of ELRs resulted in a cost reduction of €11.30 for each percentage point of increase in diagnostic yield.

Another usual clinical application of these devices is in patients with stroke of unknown etiology. It has been demonstrated that the use of these devices in patients with cryptogenic stroke, compared with the usual strategy of conventional follow-up and 24- or 48-h Holter monitoring, increases the detection rate of silent AF, allowing oral anticoagulation to be started in a greater proportion of patients and at an earlier stage[19,49,75-77].

(2) ILRs: These are small devices that are implanted subcutaneously, usually in the left parasternal region[8,25]. These devices allow for a more prolonged continuous monitoring of up to 3 to 4 years. They offer a single-lead ECG recording. The patient can activate the device when symptoms are experienced using a small remote control or through a smartphone application. Like the external devices, they use automatic arrhythmia detection algorithms[18,33]. The devices available on the market also offer a platform for remote monitoring of the events recorded, sometimes also with data transmission to the patient's mobile[20,26,32].

They have the disadvantage of being minimally invasive, since the latest models have been made significantly smaller. They require a brief surgical procedure for their implantation. There are complications in a small percentage of patients requiring the device to be withdrawn, ranging from local infection/hematoma to intolerance[78,79]. Another limitation is the price of the device, which is significantly greater than that of ELRs[25,29].

In recent years, there has been abundant literature on the diagnostic yield of implantable recording devices. The greatest experience with this kind of device concerns patients with syncope of unknown etiology[10-12], given the long monitoring time that they offer, with diagnostic yield figures around 35%[9,18,30,70]. There are also numerous papers analyzing the role of ILRs in patients with stroke of unknown etiology, and, as with ELRs, it has been shown that the strategy of implanting an ILR leads to a greater and earlier diagnosis rate than following a conventional strategy[49, 80]. They are also used in risk stratification and follow-up of certain patients[13-16,81, 82]

In the field of palpitations, their use has been more limited due to their cost and the availability of noninvasive and cheaper alternatives[83]. The recurrent unexplained palpitations study[29] compared an ILR with a conventional strategy, confirming a notably superior diagnostic yield in the ILR group (73% *vs* 21%). Despite the higher initial cost, the cost *per* diagnosis in the ILR group was lower than in the conventional strategy group (€3056 ± 363 *vs* €6768 ± 6672, $P = 0.012$). However, with the appearance on the market of new ELR devices with good diagnostic yield figures, the use of ILRs is reserved for select cases.

Outpatient telemetry monitoring: These are external monitoring devices similar to Holter monitors or cutaneous patches, but which send a continuous recording *via* telemetry to a central site where the ECG trace can be reviewed in real-time in the event of the onset of symptoms[38,58]. Subsequently, the information can be sent to medical centers with a greater or lesser degree of urgency[8]. Like the skin patches, their use varies according to the region and they are not available in all countries. The most common indication tends to be to monitor for the presence of AF after ablation procedures or to monitor the presence of significant arrhythmias following cardiac surgery or transcatheter aortic valve implantation[8]. Some records have demonstrated the greater efficacy and efficiency of this method compared with conventional Holter monitors[84].

Intracardiac devices: Despite intracardiac devices (pacemakers, defibrillators or resynchronizers) not being indicated for the purpose of monitoring, it should be mentioned that they are also useful for the work-up of patients with palpitations in cases where patients have one of these devices for another indication, since they offer a recording of the intracavitary electrogram during the episode. Many devices have

algorithms that automatically record these events allowing for their subsequent analysis. As such, it is not an ECG recording, but in the case of dual chamber devices, information can be obtained regarding the start of the event and the AV synchrony during tachycardia[85-87].

WORK-UP OF PATIENTS WITH PALPITATIONS

The aim of this section is to provide some clues to help physicians manage patients with palpitations, focusing on the proper use of electrocardiographic monitoring systems. However, it is mandatory to make a brief reference to other important aspects for the evaluation and management of these patients.

Clinical evaluation and risk stratification

The sensation of palpitations is a nonspecific symptom with multiple causes, which are not only cardiological. As such, it is essential to take an appropriate medical history to guide us towards a given suspected diagnosis, allowing us to choose the most suitable tests.

It is important to ask about the patient's medical history (systemic diseases, cardiological history, drug-abuse history, family history of sudden death, *etc.*). Similarly, it is relevant to ask about the characteristics of the palpitations: Are they sustained over time or not, or are they regular (sinus tachycardia, paroxysmal supraventricular tachycardia) or irregular (AF). The triggers (onset at rest or during physical exertion or with stressors) and the presence of certain accompanying characteristics (such as autonomic symptoms, syncope or anginal chest pain) are helpful in identifying at-risk patients requiring admission or more urgent monitoring[1,3].

The physical examination and other easily accessed complementary tests such as electrocardiography can offer specific data but with low sensitivity[1,88]. For example, the presence of a normal ECG does not exclude the presence of causes or arrhythmias, but any pathological findings do greatly increase the likelihood that the cause of the palpitations was cardiological. In up to 27% of patients, the ECG is the key to the diagnosis[88].

Thus, the initial assessment usually includes a detailed clinical history, a focused physical examination, a baseline ECG and usually also a general blood test including thyroid hormones. It is not uncommon in cardiology consultations to also systematically request an echocardiogram to rule out structural heart disease, although this may not be necessary in patients with no other risk factors for heart disease with symptoms highly suggestive of a nonrhythmic origin.

Selection of monitoring type

A key point after risk stratification is appropriately selecting the type of monitoring to be used among all the available devices, in order to achieve optimized diagnostic yield and efficiency in the patient in question.

In the field of palpitations, it is essential to correlate the patient's symptoms with the electrocardiographic recordings to reach an objective diagnosis[2,6]. This point is worthy of special mention, because it is not uncommon for patients with palpitations to experience different sensations that may correspond to different disorders. For example, it is not unusual for patients to have a sensation of a single palpitation lasting a few seconds almost every day, but to also report occasional episodes of sustained rapid palpitations that start and end suddenly. If, using a Holter monitor, we record an atrial extrasystole and relate this to the single palpitation sensation, we cannot rule out the possibility that these extrasystoles trigger episodes of paroxysmal supraventricular tachycardia (which would explain the second, less frequent, symptom). It would be an error to attribute the entirety of the patient's clinical presentation to the extrasystole, and we should select a monitoring method allowing us to record the less frequent symptom (which is the one suggestive of greater clinical importance). As such, it is essential to take a meticulous history of the symptoms experienced by the patient during monitoring before establishing a certain diagnosis[1,29].

As noted in the previous section, we currently have a wide range of devices at our disposal with significant differentiating characteristics. Various aspects must be considered. The first, and probably the most important, is the frequency with which the symptoms are experienced. The monitoring time must be in line with this frequency. As such, ideally, a 24-h Holter monitor should only be indicated in patients

with frequent and almost daily symptoms[22,48]. If the symptoms are monthly or bimonthly, ELRs have shown excellent diagnostic cost-effectiveness and have certain advantages over other devices[2,54], such as obtaining information regarding the start of the episode. In the event of more infrequent symptoms, at present, external PER are probably the device of choice.

Another important factor is device availability. Many of the new devices are not yet offered as a usual diagnostic tool at healthcare centers or are not covered by insurers. If the patient cannot fund the device, we must choose from among those we have available.

Patient comfort, cost, the accuracy of the automatic algorithms, the possibility of carrying out telemetry monitoring, and the need or otherwise to be able to record the start of the episode are other factors that may influence our decision[8].

Finally, it should be pointed out that, within a specific group of devices, it is important to ensure that the model selected has suitable technical characteristics providing a good quality recording.

Electrophysiological study

Although it is not the reason for this review, it should be mentioned that electrophysiological study (EPS) is an important diagnostic tool in managing patients with palpitations[1,89,90]. In addition to allowing for a precise diagnosis of certain arrhythmias (such as paroxysmal supraventricular tachycardias), it is possible to treat the arrhythmia with ablation during the procedure in those cases where it is indicated [91-93]. It also allows to evaluate other causes of syncope if present[9,10,94,95], and performing risk stratification in patients with structural heart disease[14,71]. Since it is an invasive test, it tends to be considered at the end of the diagnostic process, either in patients with a high probability of significant arrhythmia when the monitoring methods have not allowed for it to be documented, or in patients where, after documenting the clinical arrhythmia, ablation treatment is planned. Nonetheless, it may be indicated at an early stage in patients with recurrent palpitations whose clinical characteristics are highly suggestive of paroxysmal supraventricular tachycardia and who, as such, can benefit from ablation[1,88,89,96].

The diagnostic yield of electrophysiology study is greater in patients with structural heart disease and in those with clinical symptoms highly suggestive of paroxysmal supraventricular tachycardia. For example, in a study carried out by Valles *et al*[90] on patients with sustained palpitations that did not appear on monitoring, the diagnostic yield was 50%. Other papers have reported yields between 40% and 66%[1,89].

In any case, in our opinion, prescribing an electrophysiology study should not preclude the need for electrocardiographic monitoring during the waiting time, be it *via* telemetry monitoring systems if the patient is admitted, or with an external device if not.

Other tests

Exercise-stress testing can be useful and should be considered from the outset when patients report palpitations on exertion[1,97]. Magnetic resonance imaging, coronary computed tomography, specific hormonal studies, *etc*. should be tailored to the patient in line with clinical suspicion and will be necessary in a minority of cases.

Palpitations management work-up summary

Figure 4 summarizes the proposed general algorithm for the management of patients with palpitations of unknown etiology. This algorithm offers an overview of the issue, although it can and should be adapted in specific cases and according to the availability of tests at the center.

The first step in all patients is to perform an initial clinical assessment and stratify the risk (as stated in section ***Clinical evaluation and risk stratification***). In those patients with high-risk criteria and/or priority for EPS, it is necessary to prioritize tests and indicate the study in most cases. During the waiting period, a monitoring system should be maintained (telemetry if the patient is admitted or an ELR if it is an outpatient), because this may provide the diagnosis faster and obtain relevant information for the rest of the work-up.

In cases without risk factors (which form the majority of cases), and without a diagnosis, it is necessary to select a monitoring system, following the indications in section ***Selection of monitoring type***.

Patients without heart disease and with sporadic symptoms not suggestive of an arrhythmic origin may not require further cardiological tests. However, it is not uncommon for the clinical symptoms to continue to generate a high degree of anxiety,

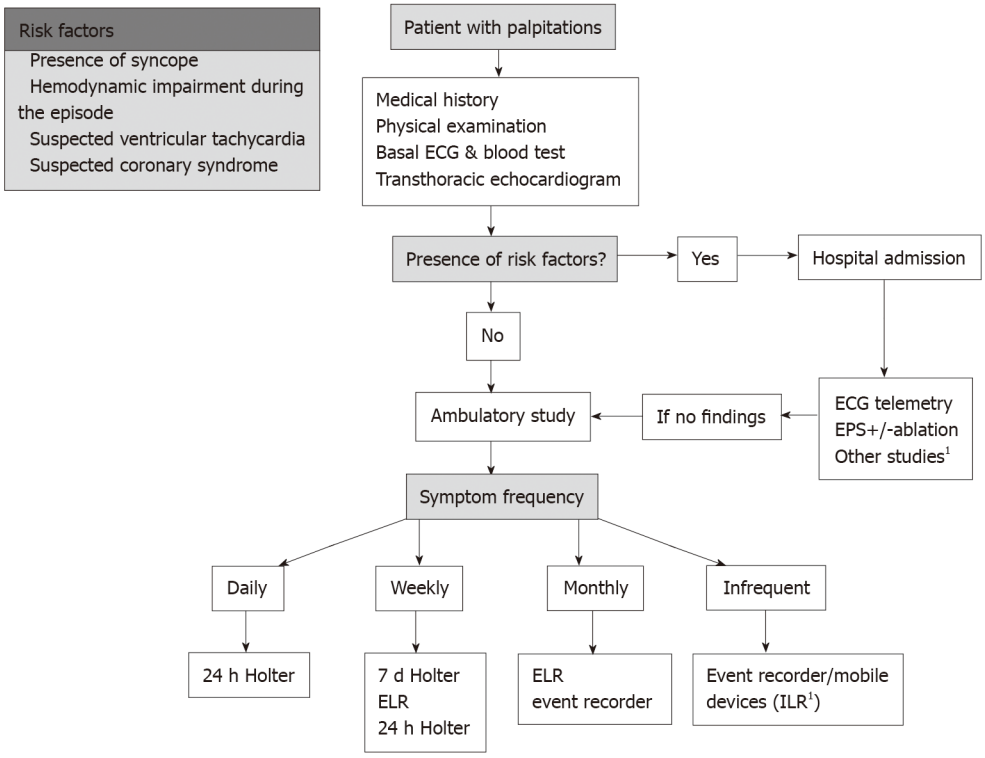

Figure 4 Proposed general algorithm for the management of patients with palpitations of unknown etiology. [1]Consider only in selected patients. ELR: External loop recorder; ILR: Implantable loop recorder; ECG: Electrocardiogram.

hence in some cases we may consider monitoring to ensure there are no arrhythmias, to reassure the patient and to avoid other futile investigations and consultations.

FUTURE PERSPECTIVE

Technological evolution shows no signs of slowing down and it is likely that monitoring devices will continue to be developed at high speed. We expect more widespread use of wearable devices, which incorporate sensors for other vital signs, to open the doors to other indications for monitoring. With regard to electrocardiographic monitoring specifically, we expect further work to be done to improve the current limitations. On the one hand, developing reliable devices that allow for quality external, comfortable, and long-lasting monitoring. On the other hand, the current recorders continue to produce a high number of artifacts and nonsignificant disorders, hence the development of software with algorithms to improve this area will be of clinical utility. The incorporation of artificial intelligence technology allowing for the prediction of future events is another of the most pioneering lines of research[98-102].

Without a doubt, technological development will help us improve the diagnosis and follow-up of patients with palpitations and other cardiac conditions. However, we must be cautious about the increasingly frequent nonmedical use of these devices. We healthcare professionals are faced with the challenge of how to manage, interpret and integrate into the healthcare system all the information that these new devices are providing.

CONCLUSION

Electrocardiographic cardiac monitoring devices are a useful diagnostic tool in confirming or excluding arrhythmias in patients with palpitations. In recent years, electrocardiographic monitoring systems have incorporated many technical improvements and many new devices are now available on the market. To achieve the best diagnostic yield and efficiency, a key point is to properly select the type of monitoring to be used among all available devices. This review provides an update on the different monitoring methods currently available, highlighting their indications

and limitations, to help healthcare professionals to appropriately select and use them in the work-up of patients with palpitations.

ACKNOWLEDGMENTS

The authors would like to thank Mr. S. Venegas for his help with the illustrations and graphics.

REFERENCES

1 **Raviele A**, Giada F, Bergfeldt L, Blanc JJ, Blomstrom-Lundqvist C, Mont L, Morgan JM, Raatikainen MJ, Steinbeck G, Viskin S, Kirchhof P, Braunschweig F, Borggrefe M, Hocini M, Della Bella P, Shah DC; European Heart Rhythm Association. Management of patients with palpitations: a position paper from the European Heart Rhythm Association. *Europace* 2011; **13**: 920-934 [PMID: 21697315 DOI: 10.1093/europace/eur130]

2 **Francisco-Pascual J**, Santos-Ortega A, Roca-Luque I, Rivas-Gándara N, Pérez-Rodón J, Milà-Pascual L, García-Dorado D, Moya-Mitjans À. Diagnostic Yield and Economic Assessment of a Diagnostic Protocol With Systematic Use of an External Loop Recorder for Patients With Palpitations. *Rev Esp Cardiol (Engl Ed)* 2019; **72**: 473-478 [PMID: 29805092 DOI: 10.1016/j.rec.2018.04.007]

3 **Weinstock C**, Wagner H, Snuckel M, Katz M. Evidence-Based Approach to Palpitations. *Med Clin North Am* 2021; **105**: 93-106 [PMID: 33246525 DOI: 10.1016/j.mcna.2020.09.004]

4 **Weber BE**, Kapoor WN. Evaluation and outcomes of patients with palpitations. *Am J Med* 1996; **100**: 138-148 [PMID: 8629647 DOI: 10.1016/s0002-9343(97)89451-x]

5 **Hoefman E**, Boer KR, van Weert HC, Reitsma JB, Koster RW, Bindels PJ. Predictive value of history taking and physical examination in diagnosing arrhythmias in general practice. *Fam Pract* 2007; **24**: 636-641 [PMID: 17986627 DOI: 10.1093/fampra/cmm056]

6 **Hoefman E**, Bindels PJ, van Weert HC. Efficacy of diagnostic tools for detecting cardiac arrhythmias: systematic literature search. *Neth Heart J* 2010; **18**: 543-551 [PMID: 21113379 DOI: 10.1007/s12471-010-0831-0]

7 Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; **93**: 1043-1065 [PMID: 8598068 DOI: 10.1161/01.cir.93.5.1043]

8 **Steinberg JS**, Varma N, Cygankiewicz I, Aziz P, Balsam P, Baranchuk A, Cantillon DJ, Dilaveris P, Dubner SJ, El-Sherif N, Krol J, Kurpesa M, La Rovere MT, Lobodzinski SS, Locati ET, Mittal S, Olshansky B, Piotrowicz E, Saxon L, Stone PH, Tereshchenko L, Turitto G, Wimmer NJ, Verrier RL, Zareba W, Piotrowicz R. 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry. *Heart Rhythm* 2017; **14**: e55-e96 [PMID: 28495301 DOI: 10.1016/j.hrthm.2017.03.038]

9 **Moya A**, Rivas-Gandara N, Perez-Rodón J, Franciso-Pascual J, Santos-Ortega A, Fumero P, Roca-Luque I. Syncope and bundle branch block : Diagnostic approach. *Herzschrittmacherther Elektrophysiol* 2018; **29**: 161-165 [PMID: 29696347 DOI: 10.1007/s00399-018-0560-4]

10 **Brignole M**, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martín A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG; ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018; **39**: 1883-1948 [PMID: 29562304 DOI: 10.1093/eurheartj/ehy037]

11 **Francisco-Pascual J**, Rodenas E, Belahnech Y, Rivas-Gándara N, Pérez-Rodon J, Santos-Ortega A, Benito B, Roca-Luque I, Cossio-Gil Y, Serra Garcia V, Llerena-Butron S, Rodríguez-García J, Moya-Mitjans A, García-Dorado D, Ferreira-González I. Syncope in Patients With Severe Aortic Stenosis: More Than Just an Obstruction Issue. *Can J Cardiol* 2021; **37**: 284-291 [PMID: 32439473 DOI: 10.1016/j.cjca.2020.04.047]

12 **Roca-Luque I**, Francisco-Pascual J, Oristrell G, Rodríguez-García J, Santos-Ortega A, Martin-Sanchez G, Rivas-Gandara N, Perez-Rodon J, Ferreira-Gonzalez I, García-Dorado D, Moya-Mitjans A. Syncope, conduction disturbance, and negative electrophysiological test: Predictive factors and risk score to predict pacemaker implantation during follow-up. *Heart Rhythm* 2019; **16**: 905-912 [PMID: 30576876 DOI: 10.1016/j.hrthm.2018.12.015]

13 **Rodés-Cabau J**, Urena M, Nombela-Franco L, Amat-Santos I, Kleiman N, Munoz-Garcia A, Atienza F, Serra V, Deyell MW, Veiga-Fernandez G, Masson JB, Canadas-Godoy V, Himbert D, Castrodeza J, Elizaga J, Francisco Pascual J, Webb JG, de la Torre JM, Asmarats L, Pelletier-Beaumont E, Philippon F. Arrhythmic Burden as Determined by Ambulatory Continuous Cardiac Monitoring in Patients With New-Onset Persistent Left Bundle Branch Block Following Transcatheter Aortic Valve Replacement: The MARE Study. *JACC Cardiovasc Interv* 2018; **11**: 1495-1505 [PMID: 30031719 DOI: 10.1016/j.jcin.2018.04.016]

14 **Rivas-Gándara N**, Francisco-Pascual J, Pijuan-Domenech A, Ribera-Solé A, Dos-Subirá L, Benito

B, Terricabras M, Pérez-Rodon J, Subirana MT, Santos-Ortega A, Roses-Noguer F, Miranda B, Moya-Mitjans À, Ferreira-González I. Risk stratification of ventricular arrhythmias in repaired tetralogy of Fallot. *Rev Esp Cardiol (Engl Ed)* 2021 [PMID: 33461928 DOI: 10.1016/j.rec.2020.12.003]

15 **Nielsen JC**, Lin YJ, de Oliveira Figueiredo MJ, Sepehri Shamloo A, Alfie A, Boveda S, Dagres N, Di Toro D, Eckhardt LL, Ellenbogen K, Hardy C, Ikeda T, Jaswal A, Kaufman E, Krahn A, Kusano K, Kutyifa V, S Lim H, Lip GYH, Nava-Townsend S, Pak HN, Rodríguez Diez G, Sauer W, Saxena A, Svendsen JH, Vanegas D, Vaseghi M, Wilde A, Bunch TJ, Buxton AE, Calvimontes G, Chao TF, Eckardt L, Estner H, Gillis AM, Isa R, Kautzner J, Maury P, Moss JD, Nam GB, Olshansky B, Molano LFP, Pimentel M, Prabhu M, Tzou WS, Sommer P, Swampillai J, Vidal A, Deneke T, Hindricks G, Leclercq C. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. *J Arrhythm* 2020; **36**: 553-607 [PMID: 32782627 DOI: 10.1002/joa3.12338]

16 **Palà E**, Pagola J, Juega J, Francisco-Pascual J, Bustamante A, Penalba A, Comas I, Rodriguez M, De Lera Alfonso M, Arenillas JF, de Torres R, Pérez-Sánchez S, Cabezas JA, Moniche F, González-Alujas T, Molina CA, Montaner J. B-type natriuretic peptide over N-terminal pro-brain natriuretic peptide to predict incident atrial fibrillation after cryptogenic stroke. *Eur J Neurol* 2021; **28**: 540-547 [PMID: 33043545 DOI: 10.1111/ene.14579]

17 **Galli A**, Ambrosini F, Lombardi F. Holter Monitoring and Loop Recorders: From Research to Clinical Practice. *Arrhythm Electrophysiol Rev* 2016; **5**: 136-143 [PMID: 27617093 DOI: 10.15420/AER.2016.17.2]

18 **Francisco-Pascual J**, Olivella San Emeterio A, Rivas-Gándara N, Pérez-Rodón J, Benito B, Santos-Ortega A, Moya-Mitjans À, Rodríguez García J, Llerena Butrón SI, Cantalapiedra Romero J, Ferreira González I. High incidence of subclinical atrial fibrillation in patients with syncope monitored with implantable cardiac monitor. *Int J Cardiol* 2020; **316**: 110-116 [PMID: 32470530 DOI: 10.1016/j.ijcard.2020.05.078]

19 **Pagola J**, Juega J, Francisco-Pascual J, Moya A, Sanchis M, Bustamante A, Penalba A, Usero M, Cortijo E, Arenillas JF, Calleja AI, Sandin-Fuentes M, Rubio J, Mancha F, Escudero-Martinez I, Moniche F, de Torres R, Pérez-Sánchez S, González-Matos CE, Vega Á, Pedrote AA, Arana-Rueda E, Montaner J, Molina CA; CryptoAF investigators. Yield of atrial fibrillation detection with Textile Wearable Holter from the acute phase of stroke: Pilot study of Crypto-AF registry. *Int J Cardiol* 2018; **251**: 45-50 [PMID: 29107360 DOI: 10.1016/j.ijcard.2017.10.063]

20 **Francisco-Pascual J**, Rivas-Gándara N, Santos-Ortega A, Pérez-Rodón J, Benito B, Belahnech Y, Ferreira-González I. [Cardiac biometric variables and arrhythmic events during COVID-19 pandemic lockdown in patients with an implantable cardiac monitor for syncope work-up]. *Med Clin (Barc)* 2021; **156**: 496-499 [PMID: 33642036 DOI: 10.1016/j.medcli.2020.12.005]

21 **Muntané-Carol G**, Urena M, Nombela-Franco L, Amat-Santos I, Kleiman N, Munoz-Garcia A, Atienza F, Serra V, Deyell MW, Veiga-Fernandez G, Masson JB, Canadas-Godoy V, Himbert D, Castrodeza J, Elizaga J, Francisco Pascual J, Webb JG, de la Torre Hernandez JM, Asmarats L, Pelletier-Beaumont E, Philippon F, Rodés-Cabau J. Arrhythmic burden in patients with new-onset persistent left bundle branch block after transcatheter aortic valve replacement: 2-year results of the MARE study. *Europace* 2021; **23**: 254-263 [PMID: 33083813 DOI: 10.1093/europace/euaa213]

22 **Sulfi S**, Balami D, Sekhri N, Suliman A, Kapur A, Archbold RA, Ranjadayalan K, Timmis AD. Limited clinical utility of Holter monitoring in patients with palpitations or altered consciousness: analysis of 8973 recordings in 7394 patients. *Ann Noninvasive Electrocardiol* 2008; **13**: 39-43 [PMID: 18234005 DOI: 10.1111/j.1542-474X.2007.00199.x]

23 **Mittal S**, Movsowitz C, Steinberg JS. Ambulatory external electrocardiographic monitoring: focus on atrial fibrillation. *J Am Coll Cardiol* 2011; **58**: 1741-1749 [PMID: 21996384 DOI: 10.1016/j.jacc.2011.07.026]

24 **Sana F**, Isselbacher EM, Singh JP, Heist EK, Pathik B, Armoundas AA. Wearable Devices for Ambulatory Cardiac Monitoring: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; **75**: 1582-1592 [PMID: 32241375 DOI: 10.1016/j.jacc.2020.01.046]

25 **Task Force members**. , Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, Sulke N, Wieling W; EHRA Scientific Documents Committee, Auricchio A, Lip GY, Almendral J, Kirchhof P, Aliot E, Gasparini M, Braunschweig F; Document Reviewers, Lip GY, Almendral J, Kirchhof P, Botto GL; EHRA Scientific Documents Committee. Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009; **11**: 671-687 [PMID: 19401342 DOI: 10.1093/europace/eup097]

26 **Kohno R**, Nantsupawat T, Benditt DG. Trends in Subcutaneous Cardiac Monitoring Technology. *J Innov Card Rhythm Manag* 2018; **9**: 3247-3255 [PMID: 32494499 DOI: 10.19102/icrm.2018.090703]

27 **Zimetbaum P**, Goldman A. Ambulatory arrhythmia monitoring: choosing the right device. *Circulation* 2010; **122**: 1629-1636 [PMID: 20956237 DOI: 10.1161/CIRCULATIONAHA.109.925610]

28 **de Asmundis C**, Conte G, Sieira J, Chierchia GB, Rodriguez-Manero M, Di Giovanni G, Ciconte G, Levinstein M, Baltogiannis G, Saitoh Y, Casado-Arroyo R, Brugada P. Comparison of the patient-activated event recording system vs. traditional 24 h Holter electrocardiography in individuals with

paroxysmal palpitations or dizziness. *Europace* 2014; **16**: 1231-1235 [PMID: 24574492 DOI: 10.1093/europace/eut411]

29 **Giada F**, Gulizia M, Francese M, Croci F, Santangelo L, Santomauro M, Occhetta E, Menozzi C, Raviele A. Recurrent unexplained palpitations (RUP) study comparison of implantable loop recorder versus conventional diagnostic strategy. *J Am Coll Cardiol* 2007; **49**: 1951-1956 [PMID: 17498580 DOI: 10.1016/j.jacc.2007.02.036]

30 **Fogel RI**, Evans JJ, Prystowsky EN. Utility and cost of event recorders in the diagnosis of palpitations, presyncope, and syncope. *Am J Cardiol* 1997; **79**: 207-208 [PMID: 9193028 DOI: 10.1016/s0002-9149(96)00717-5]

31 **Mason JW**, Hancock EW, Gettes LS; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society, Bailey JJ, Childers R, Deal BJ, Josephson M, Kligfield P, Kors JA, Macfarlane P, Pahlm O, Mirvis DM, Okin P, Rautaharju P, Surawicz B, van Herpen G, Wagner GS, Wellens H. Recommendations for the standardization and interpretation of the electrocardiogram: part II: Electrocardiography diagnostic statement list: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation* 2007; **115**: 1325-1332 [PMID: 17322456 DOI: 10.1161/CIRCULATIONAHA.106.180201]

32 **Moya Mitjans A**, Francisco Pascual J, Pérez Rodón J, Rivas Gándara N, Garcia-Dorado D. Nuevos avances en la monitorización electrocardiográfica prolongada: Reveal LINQ TM. [cited 10 April 2021]. Available from: https://www.researchgate.net/publication/281176697_Nuevos_avances_en_la_monitorizacion_electrocardiografica_prolongada_Reveal_LINQ_TM

33 **Sanders P**, Pürerfellner H, Pokushalov E, Sarkar S, Di Bacco M, Maus B, Dekker LR; Reveal LINQ Usability Investigators. Performance of a new atrial fibrillation detection algorithm in a miniaturized insertable cardiac monitor: Results from the Reveal LINQ Usability Study. *Heart Rhythm* 2016; **13**: 1425-1430 [PMID: 26961298 DOI: 10.1016/j.hrthm.2016.03.005]

34 **Balsam P**, Lodziński P, Tymińska A, Ozierański K, Januszkiewicz Ł, Główczyńska R, Wesołowska K, Peller M, Pietrzak R, Książczyk T, Borodzicz S, Kołtowski Ł, Borkowski M, Werner B, Opolski G, Grabowski M. Study design and rationale for biomedical shirt-based electrocardiography monitoring in relevant clinical situations: ECG-shirt study. *Cardiol J* 2018; **25**: 52-59 [PMID: 28840587 DOI: 10.5603/CJ.a2017.0102]

35 **Steinberg C**, Philippon F, Sanchez M, Fortier-Poisson P, O'Hara G, Molin F, Sarrazin JF, Nault I, Blier L, Roy K, Plourde B, Champagne J. A Novel Wearable Device for Continuous Ambulatory ECG Recording: Proof of Concept and Assessment of Signal Quality. *Biosensors (Basel)* 2019; **9** [PMID: 30669678 DOI: 10.3390/bios9010017]

36 **Welinder A**, Wagner GS, Maynard C, Pahlm O. Differences in QRS axis measurements, classification of inferior myocardial infarction, and noise tolerance for 12-lead electrocardiograms acquired from monitoring electrode positions compared to standard locations. *Am J Cardiol* 2010; **106**: 581-586 [PMID: 20691320 DOI: 10.1016/j.amjcard.2010.03.073]

37 **Brockway R**, Brockway M, Brockway B, Hamlin R. Comparison of one- and three-lead ECG to measure cardiac intervals and differentiate drug-induced multi-channel block. *J Pharmacol Toxicol Methods* 2018; **93**: 80-89 [PMID: 29704608 DOI: 10.1016/j.vascn.2018.04.004]

38 **Engel JM**, Chakravarthy N, Katra RP, Mazar S, Libbus I, Chavan A. Estimation of patient compliance in application of adherent mobile cardiac telemetry device. *Annu Int Conf IEEE Eng Med Biol Soc* 2011; **2011**: 1536-1539 [PMID: 22254613 DOI: 10.1109/IEMBS.2011.6090448]

39 **Heilbron EL**. Advances in modern electrocardiographic equipment for long-term ambulatory monitoring. *Card Electrophysiol Rev* 2002; **6**: 185-189 [PMID: 12114836 DOI: 10.1023/a:1016322218490]

40 **Perez MV**, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, Hung G, Lee J, Kowey P, Talati N, Nag D, Gummidipundi SE, Beatty A, Hills MT, Desai S, Granger CB, Desai M, Turakhia MP; Apple Heart Study Investigators. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med* 2019; **381**: 1909-1917 [PMID: 31722151 DOI: 10.1056/NEJMoa1901183]

41 **Wegner FK**, Kochhäuser S, Ellermann C, Lange PS, Frommeyer G, Leitz P, Eckardt L, Dechering DG. Prospective blinded Evaluation of the smartphone-based AliveCor Kardia ECG monitor for Atrial Fibrillation detection: The PEAK-AF study. *Eur J Intern Med* 2020; **73**: 72-75 [PMID: 31806411 DOI: 10.1016/j.ejim.2019.11.018]

42 **Kinlay S**, Leitch JW, Neil A, Chapman BL, Hardy DB, Fletcher PJ. Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations. A controlled clinical trial. *Ann Intern Med* 1996; **124**: 16-20 [PMID: 7503472 DOI: 10.7326/0003-4819-124-1_part_1-199601010-00003]

43 **Attanasio P**, Huemer M, Loehr L, Parwani AS, Boldt LH, Haverkamp W, Wutzler A. Use of a Patient-Activated Event Recording System in Patients with Tachycardic Palpitations: How Long to Follow Up? *Ann Noninvasive Electrocardiol* 2015; **20**: 566-569 [PMID: 26246467 DOI: 10.1111/anec.12301]

44 **Rischard J**, Waldmann V, Moulin T, Sharifzadehgan A, Lee R, Narayanan K, Garcia R, Marijon E. Assessment of Heart Rhythm Disorders Using the AliveCor Heart Monitor: Beyond the Detection of Atrial Fibrillation. *JACC Clin Electrophysiol* 2020; **6**: 1313-1315 [PMID: 33092760 DOI:

10.1016/j.jacep.2020.05.007]
45 **Beltrame T**, Amelard R, Wong A, Hughson RL. Extracting aerobic system dynamics during unsupervised activities of daily living using wearable sensor machine learning models. *J Appl Physiol (1985)* 2018; **124**: 473-481 [PMID: 28596271 DOI: 10.1152/japplphysiol.00299.2017]
46 **Hu Y**, Kim EG, Cao G, Liu S, Xu Y. Physiological acoustic sensing based on accelerometers: a survey for mobile healthcare. *Ann Biomed Eng* 2014; **42**: 2264-2277 [PMID: 25234130 DOI: 10.1007/s10439-014-1111-8]
47 **Palma Gámiz JL**, Arribas Jiménez A, González Juanatey JR, Marín Huerta E, Martín-Ambrosio ES. [Spanish Society of Cardiology practice guidelines on ambulatory monitoring of electrocardiogram and blood pressure]. *Rev Esp Cardiol* 2000; **53**: 91-109 [PMID: 10701326 DOI: 10.1016/s0300-8932(00)75066-4]
48 **Su L**, Borov S, Zrenner B. 12-lead Holter electrocardiography. Review of the literature and clinical application update. *Herzschrittmacherther Elektrophysiol* 2013; **24**: 92-96 [PMID: 23778563 DOI: 10.1007/s00399-013-0268-4]
49 **PérezRodon J**, FranciscoPascual J, RivasGándara N, RocaLuque I, Bellera N, MoyaMitjans À. Cryptogenic Stroke And Role Of Loop Recorder. *J Atr Fibrillation* 2014; **7**: 1178 [PMID: 27957141 DOI: 10.4022/jafib.1178]
50 **Stojkovic S**, Ristl R, Moser FT, Wolzt M, Wojta J, Schmidinger H, Pezawas T. T-wave variability for the prediction of fast ventricular arrhythmias – prospective, observer-blind study. *Circ J* 2015; **79**: 318-324 [PMID: 25482297 DOI: 10.1253/circj.CJ-14-1028]
51 **Follansbee CW**, Beerman L, Arora G. Automated QT analysis on Holter monitors in pediatric patients can differentiate long QT syndrome from controls. *Pacing Clin Electrophysiol* 2018; **41**: 50-56 [PMID: 29219203 DOI: 10.1111/pace.13244]
52 **Casas G**, Rivas-Gándara N, Francisco-Pascual J, Moya-Mitjans À, García-Dorado D. Postural Orthostatic Tachycardia Syndrome and Vasospastic Angina: Therapeutic Approach to a Previously Unreported Association. *Rev Esp Cardiol (Engl Ed)* 2019; **72**: 509-510 [PMID: 30322723 DOI: 10.1016/j.rec.2018.05.043]
53 **Roca-Luque I**, Rivas-Gándara N, Dos Subirà L, Francisco Pascual J, Pijuan-Domenech A, Pérez-Rodon J, Subirana-Domenech MT, Santos-Ortega A, Rosés-Noguer F, Miranda-Barrio B, Ferreira-Gonzalez I, Casaldàliga Ferrer J, García-Dorado García D, Moya Mitjans A. Long-Term Follow-Up After Ablation of Intra-Atrial Re-Entrant Tachycardia in Patients With Congenital Heart Disease: Types and Predictors of Recurrence. *JACC Clin Electrophysiol* 2018; **4**: 771-780 [PMID: 29929671 DOI: 10.1016/j.jacep.2018.04.011]
54 **Locati ET**, Moya A, Oliveira M, Tanner H, Willems R, Lunati M, Brignole M. External prolonged electrocardiogram monitoring in unexplained syncope and palpitations: results of the SYNARR-Flash study. *Europace* 2016; **18**: 1265-1272 [PMID: 26519025 DOI: 10.1093/europace/euv311]
55 **Lobodzinski SS**. ECG patch monitors for assessment of cardiac rhythm abnormalities. *Prog Cardiovasc Dis* 2013; **56**: 224-229 [PMID: 24215754 DOI: 10.1016/j.pcad.2013.08.006]
56 **Yenikomshian M**, Jarvis J, Patton C, Yee C, Mortimer R, Birnbaum H, Topash M. Cardiac arrhythmia detection outcomes among patients monitored with the Zio patch system: a systematic literature review. *Curr Med Res Opin* 2019; **35**: 1659-1670 [PMID: 31045463 DOI: 10.1080/03007995.2019.1610370]
57 **Murali S**, Brugger N, Rincon F, Mashru M, Cook S, Goy JJ. Cardiac Ambulatory Monitoring: New Wireless Device Validated Against Conventional Holter Monitoring in a Case Series. *Front Cardiovasc Med* 2020; **7**: 587945 [PMID: 33330650 DOI: 10.3389/fcvm.2020.587945]
58 **Engel JM**, Mehta V, Fogoros R, Chavan A. Study of arrhythmia prevalence in NUVANT Mobile Cardiac Telemetry system patients. *Annu Int Conf IEEE Eng Med Biol Soc* 2012; **2012**: 2440-2443 [PMID: 23366418 DOI: 10.1109/EMBC.2012.6346457]
59 **Barrett PM**, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, Fought AJ, Topol EJ. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. *Am J Med* 2014; **127**: 95.e11-95.e17 [PMID: 24384108 DOI: 10.1016/j.amjmed.2013.10.003]
60 **Soroudi A**, Hernández N, Berglin L, Nierstrasz V. Electrode placement in electrocardiography smart garments: A review. *J Electrocardiol* 2019; **57**: 27-30 [PMID: 31473476 DOI: 10.1016/j.jelectrocard.2019.08.015]
61 **Cho H**, Lee JH. A Study on the Optimal Positions of ECG Electrodes in a Garment for the Design of ECG-Monitoring Clothing for Male. *J Med Syst* 2015; **39**: 95 [PMID: 26254250 DOI: 10.1007/s10916-015-0279-2]
62 **Myerburg RJ**. The Screening ECG and Cardiac Risks. *JAMA* 2018; **319**: 2277-2279 [PMID: 29896615 DOI: 10.1001/jama.2018.6766]
63 **Hall A**, Mitchell ARJ, Wood L, Holland C. Effectiveness of a single lead AliveCor electrocardiogram application for the screening of atrial fibrillation: A systematic review. *Medicine (Baltimore)* 2020; **99**: e21388 [PMID: 32791751 DOI: 10.1097/MD.0000000000021388]
64 **Bumgarner JM**, Lambert CT, Hussein AA, Cantillon DJ, Baranowski B, Wolski K, Lindsay BD, Wazni OM, Tarakji KG. Smartwatch Algorithm for Automated Detection of Atrial Fibrillation. *J Am Coll Cardiol* 2018; **71**: 2381-2388 [PMID: 29535065 DOI: 10.1016/j.jacc.2018.03.003]
65 **Cobos Gil MÁ**. Standard and Precordial Leads Obtained With an Apple Watch. *Ann Intern Med* 2020; **173**: 249-250 [PMID: 32745452 DOI: 10.7326/L20-0588]
66 **Samol A**, Bischof K, Luani B, Pascut D, Wiemer M, Kaese S. Recording of Bipolar Multichannel

ECGs by a Smartwatch: Modern ECG Diagnostic 100 Years after Einthoven. *Sensors (Basel)* 2019; **19** [PMID: 31261981 DOI: 10.3390/s19132894]

67 **Spaccarotella CAM**, Polimeni A, Migliarino S, Principe E, Curcio A, Mongiardo A, Sorrentino S, De Rosa S, Indolfi C. Multichannel Electrocardiograms Obtained by a Smartwatch for the Diagnosis of ST-Segment Changes. *JAMA Cardiol* 2020; **5**: 1176-1180 [PMID: 32865545 DOI: 10.1001/jamacardio.2020.3994]

68 **Kwon S**, Lee D, Kim J, Lee Y, Kang S, Seo S, Park K. Sinabro: A Smartphone-Integrated Opportunistic Electrocardiogram Monitoring System. *Sensors (Basel)* 2016; **16** [PMID: 26978364 DOI: 10.3390/s16030361]

69 **Christiansen CS**, Gjesdal K. [Implantable loop recorders in evaluation of syncope]. *Tidsskr Nor Laegeforen* 2007; **127**: 1657-1659 [PMID: 17571107]

70 **Solano A**, Menozzi C, Maggi R, Donateo P, Bottoni N, Lolli G, Tomasi C, Croci F, Oddone D, Puggioni E, Brignole M. Incidence, diagnostic yield and safety of the implantable loop-recorder to detect the mechanism of syncope in patients with and without structural heart disease. *Eur Heart J* 2004; **25**: 1116-1119 [PMID: 15231369 DOI: 10.1016/j.ehj.2004.05.013]

71 **Francisco-Pascual J**, Rodenas-Alesina E, Rivas-Gándara N, Belahnech Y, Olivella San Emeterio A, Pérez-Rodón J, Benito B, Santos-Ortega A, Moya-Mitjans À, Casas G, Cantalapiedra-Romero J, Maldonado J, Ferreira-González I. Etiology and prognosis of patients with unexplained syncope and mid-range left ventricular dysfunction. *Heart Rhythm* 2021; **18**: 597-604 [PMID: 33326869 DOI: 10.1016/j.hrthm.2020.12.009]

72 **Rajanna RR**, Natarajan S, Prakash V, Vittala PR, Arun U, Sahoo S. External Cardiac Loop Recorders: Functionalities, Diagnostic Efficacy, Challenges and Opportunities. *IEEE Rev Biomed Eng* 2021; **PP** [PMID: 33513107 DOI: 10.1109/RBME.2021.3055219]

73 **Zimetbaum PJ**, Kim KY, Josephson ME, Goldberger AL, Cohen DJ. Diagnostic yield and optimal duration of continuous-loop event monitoring for the diagnosis of palpitations. A cost-effectiveness analysis. *Ann Intern Med* 1998; **128**: 890-895 [PMID: 9634426 DOI: 10.7326/0003-4819-128-11-199806010-00002]

74 **Schuchert A**, Maas R, Kretzschmar C, Behrens G, Kratzmann I, Meinertz T. Diagnostic yield of external electrocardiographic loop recorders in patients with recurrent syncope and negative tilt table test. *Pacing Clin Electrophysiol* 2003; **26**: 1837-1840 [PMID: 12930497 DOI: 10.1046/j.1460-9592.2003.t01-1-00277.x]

75 **Gladstone DJ**, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Côté R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014; **370**: 2467-2477 [PMID: 24963566 DOI: 10.1056/NEJMoa1311376]

76 **Pagola J**, Juega J, Francisco-Pascual J, Bustamante A, Penalba A, Pala E, Rodriguez M, De Lera-Alfonso M, Arenillas JF, Cabezas JA, Moniche F, de Torres R, Montaner J, González-Alujas T, Alvarez-Sabin J, Molina CA; Crypto-AF study group. Predicting Atrial Fibrillation with High Risk of Embolization with Atrial Strain and NT-proBNP. *Transl Stroke Res* 2021; **12**: 735-741 [PMID: 33184686 DOI: 10.1007/s12975-020-00873-2]

77 **Pagola J**, Juega J, Francisco-Pascual J, Bustamante A, Penalba A, Pala E, Rodriguez M, De Lera Alfonso M, Arenillas JF, Cabezas JA, Moniche F, de Torres R, Montaner J, González-Alujas T, Alvarez-Sabin J, Molina CA; Crypto-AF study group. Large vessel occlusion is independently associated with atrial fibrillation detection. *Eur J Neurol* 2020; **27**: 1618-1624 [PMID: 32347993 DOI: 10.1111/ene.14281]

78 **Wong GR**, Lau DH, Middeldorp ME, Harrington JA, Stolcman S, Wilson L, Twomey DJ, Kumar S, Munawar DA, Khokhar KB, Mahajan R, Sanders P. Feasibility and safety of Reveal LINQ insertion in a sterile procedure room versus electrophysiology laboratory. *Int J Cardiol* 2016; **223**: 13-17 [PMID: 27525370 DOI: 10.1016/j.ijcard.2016.08.113]

79 **Diederichsen SZ**, Haugan KJ, Højberg S, Holst AG, Køber L, Pedersen KB, Graff C, Krieger D, Brandes A, Svendsen JH. Complications after implantation of a new-generation insertable cardiac monitor: Results from the LOOP study. *Int J Cardiol* 2017; **241**: 229-234 [PMID: 28457562 DOI: 10.1016/j.ijcard.2017.03.144]

80 **Sanna T**, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; **370**: 2478-2486 [PMID: 24963567 DOI: 10.1056/NEJMoa1313600]

81 **Muntané-Carol G**, Nombela-Franco L, Serra V, Urena M, Amat-Santos I, Vilalta V, Chamandi C, Lhermusier T, Veiga-Fernandez G, Kleiman N, Canadas-Godoy V, Francisco-Pascual J, Himbert D, Castrodeza J, Fernandez-Nofrerias E, Baudinaud P, Mondoly P, Campelo-Parada F, De la Torre Hernandez JM, Pelletier-Beaumont E, Philippon F, Rodés-Cabau J. Late arrhythmias in patients with new-onset persistent left bundle branch block after transcatheter aortic valve replacement using a balloon-expandable valve. *Heart Rhythm* 2021 [PMID: 34082083 DOI: 10.1016/j.hrthm.2021.05.031]

82 **Dwivedi A**, Joza J, Malkani K, Mendelson TB, Priori SG, Chinitz LA, Fowler SJ, Cerrone M. Implantable Loop Recorder in Inherited Arrhythmia Diseases: A Critical Tool for Symptom Diagnosis and Advanced Risk Stratification. *JACC Clin Electrophysiol* 2018; **4**: 1372-1374 [PMID:

30336885 DOI: 10.1016/j.jacep.2018.07.008]
83 **Padmanabhan D**, Kancharla K, El-Harasis MA, Isath A, Makkar N, Noseworthy PA, Friedman PA, Cha YM, Kapa S. Diagnostic and therapeutic value of implantable loop recorder: A tertiary care center experience. *Pacing Clin Electrophysiol* 2019; **42**: 38-45 [PMID: 30357866 DOI: 10.1111/pace.13533]
84 **Tsang JP**, Mohan S. Benefits of monitoring patients with mobile cardiac telemetry (MCT) compared with the Event or Holter monitors. *Med Devices (Auckl)* 2013; **7**: 1-5 [PMID: 24353449 DOI: 10.2147/MDER.S54038]
85 **Healey JS**, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012; **366**: 120-129 [PMID: 22236222 DOI: 10.1056/NEJMoa1105575]
86 **Stevenson WG**, John RM. Ventricular arrhythmias in patients with implanted defibrillators. *Circulation* 2011; **124**: e411-e414 [PMID: 22007105 DOI: 10.1161/CIRCULATIONAHA.111.064816]
87 **Quirino G**, Giammaria M, Corbucci G, Pistelli P, Turri E, Mazza A, Perucca A, Checchinato C, Dalmasso M, Barold SS. Diagnosis of paroxysmal atrial fibrillation in patients with implanted pacemakers: relationship to symptoms and other variables. *Pacing Clin Electrophysiol* 2009; **32**: 91-98 [PMID: 19140918 DOI: 10.1111/j.1540-8159.2009.02181.x]
88 **Kopp DE**, Wilber DJ. Palpitations and arrhythmias. Separating the benign from the dangerous. *Postgrad Med* 1992; **91**: 241-244, 247 [PMID: 1728776 DOI: 10.1080/00325481.1992.11701180]
89 **Tsiachris D**, Koutagiar I, Gatzoulis KA, Arsenos P, Rigatou A, Dilaveris P, Sideris S, Papadopoulos A, Kritikos A, Stefanadis C, Tousoulis D. Diagnosis and management of phantom tachycardias based on an electrophysiologically guided approach. *Hellenic J Cardiol* 2016; **57**: 340-344 [PMID: 28190736 DOI: 10.1016/j.hjc.2016.11.030]
90 **Valles E**, Martí-Almor J, Bazan V, Suarez F, Cian D, Portillo L, Bruguera-Cortada J. Diagnostic and prognostic value of electrophysiologic study in patients with nondocumented palpitations. *Am J Cardiol* 2011; **107**: 1333-1337 [PMID: 21371684 DOI: 10.1016/j.amjcard.2010.12.047]
91 **Roca-Luque I**, Rivas-Gándara N, Dos-Subirà L, Francisco-Pascual J, Pijuan-Domenech A, Pérez-Rodon J, Santos-Ortega A, Roses-Noguer F, Ferreira-Gonzalez I, García-Dorado García D, Moya Mitjans A. Predictors of Acute Failure Ablation of Intra-atrial Re-entrant Tachycardia in Patients With Congenital Heart Disease: Cardiac Disease, Atypical Flutter, and Previous Atrial Fibrillation. *J Am Heart Assoc* 2018; **7** [PMID: 29602766 DOI: 10.1161/JAHA.117.008063]
92 **Pérez-Rodon J**, Rodriguez-García J, Sarrias-Merce A, Rivas-Gandara N, Roca-Luque I, Francisco-Pascual J, Santos-Ortega A, Martín-Sánchez G, Ferreira-González I, Rodríguez-Palomares J, Evangelista-Masip A, García-Dorado D, Moya-Mitjans À. Predictors of acute inefficacy and the radiofrequency energy time required for cavotricuspid isthmus-dependent atrial flutter ablation. *J Interv Card Electrophysiol* 2017; **49**: 83-91 [PMID: 28265782 DOI: 10.1007/s10840-017-0232-z]
93 **Roca-Luque I**, Rivas N, Francisco J, Perez J, Acosta G, Oristrell G, Terricabres M, Garcia-Dorado D, Moya A. Selective Angiography Using the Radiofrequency Catheter: An Alternative Technique for Mapping and Ablation in the Aortic Cusps. *J Cardiovasc Electrophysiol* 2017; **28**: 126-131 [PMID: 27759948 DOI: 10.1111/jce.13109]
94 **Roca-Luque I**, Francisco-Pasqual J, Oristrell G, Rodríguez-García J, Santos-Ortega A, Martin-Sanchez G, Rivas-Gandara N, Perez-Rodon J, Ferreira-Gonzalez I, García-Dorado D, Moya-Mitjans A. Flecainide Versus Procainamide in Electrophysiological Study in Patients With Syncope and Wide QRS Duration. *JACC Clin Electrophysiol* 2019; **5**: 212-219 [PMID: 30784693 DOI: 10.1016/j.jacep.2018.09.015]
95 **Roca-Luque I**, Oristrell G, Francisco-Pasqual J, Rodríguez-García J, Santos-Ortega A, Martin-Sanchez G, Rivas-Gandara N, Perez-Rodon J, Ferreira-Gonzalez I, García-Dorado D, Moya-Mitjans A. Predictors of positive electrophysiological study in patients with syncope and bundle branch block: PR interval and type of conduction disturbance. *Clin Cardiol* 2018; **41**: 1537-1542 [PMID: 30251426 DOI: 10.1002/clc.23079]
96 **Wilken J**. Evidence-based Recommendations for the Evaluation of Palpitations in the Primary Care Setting. *Med Clin North Am* 2016; **100**: 981-989 [PMID: 27542418 DOI: 10.1016/j.mcna.2016.04.006]
97 **Jelinek MV**, Lown B. Exercise stress testing for exposure of cardiac arrhythmia. *Prog Cardiovasc Dis* 1974; **16**: 497-522 [PMID: 4590953 DOI: 10.1016/0033-0620(74)90008-5]
98 **Schaefer JR**, Leussler D, Rosin L, Pittrow D, Hepp T. Improved detection of paroxysmal atrial fibrillation utilizing a software-assisted electrocardiogram approach. *PLoS One* 2014; **9**: e89328 [PMID: 24586692 DOI: 10.1371/journal.pone.0089328]
99 **Feeny AK**, Chung MK, Madabhushi A, Attia ZI, Cikes M, Firouznia M, Friedman PA, Kalscheur MM, Kapa S, Narayan SM, Noseworthy PA, Passman RS, Perez MV, Peters NS, Piccini JP, Tarakji KG, Thomas SA, Trayanova NA, Turakhia MP, Wang PJ. Artificial Intelligence and Machine Learning in Arrhythmias and Cardiac Electrophysiology. *Circ Arrhythm Electrophysiol* 2020; **13**: e007952 [PMID: 32628863 DOI: 10.1161/CIRCEP.119.007952]
100 **Yang M**, Zhou R, Qiu X, Feng X, Sun J, Wang Q, Lu Q, Zhang P, Liu B, Li W, Chen M, Zhao Y, Mo B, Zhou X, Zhang X, Hua Y, Guo J, Bi F, Cao Y, Ling F, Shi S, Li YG. Artificial intelligence-assisted analysis on the association between exposure to ambient fine particulate matter and incidence of arrhythmias in outpatients of Shanghai community hospitals. *Environ Int* 2020; **139**:

105745 [PMID: 32334122 DOI: 10.1016/j.envint.2020.105745]

101 **Serhani MA**, T El Kassabi H, Ismail H, Nujum Navaz A. ECG Monitoring Systems: Review, Architecture, Processes, and Key Challenges. *Sensors (Basel)* 2020; **20** [PMID: 32213969 DOI: 10.3390/s20061796]

102 **Krittanawong C**, Rogers AJ, Johnson KW, Wang Z, Turakhia MP, Halperin JL, Narayan SM. Integration of novel monitoring devices with machine learning technology for scalable cardiovascular management. *Nat Rev Cardiol* 2021; **18**: 75-91 [PMID: 33037325 DOI: 10.1038/s41569-020-00445-9]

103 **Paudel B**, Paudel K. The diagnostic significance of the holter monitoring in the evaluation of palpitation. *J Clin Diagn Res* 2013; **7**: 480-483 [PMID: 23634400 DOI: 10.7860/JCDR/2013/4923.2802]

104 **Narasimha D**, Hanna N, Beck H, Chaskes M, Glover R, Gatewood R, Bourji M, Gudleski GD, Danzer S, Curtis AB. Validation of a smartphone-based event recorder for arrhythmia detection. *Pacing Clin Electrophysiol* 2018; **41**: 487-494 [PMID: 29493801 DOI: 10.1111/pace.13317]

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 November 26; 13(11): 628-649

DOI: 10.4330/wjc.v13.i11.628

ISSN 1949-8462 (online)

MINIREVIEWS

Cardiovascular magnetic resonance of cardiac tumors and masses

Marco Gatti, Tommaso D'Angelo, Giuseppe Muscogiuri, Serena Dell'aversana, Alessandro Andreis, Andrea Carisio, Fatemeh Darvizeh, Davide Tore, Gianluca Pontone, Riccardo Faletti

ORCID number: Marco Gatti 0000-0001-8168-5280; Tommaso D'Angelo 0000-0003-0004-6378; Giuseppe Muscogiuri 0000-0003-4757-2420; Serena Dell'aversana 0000-0002-5958-2346; Alessandro Andreis 0000-0002-1203-000X; Andrea Carisio 0000-0003-3957-7934; Fatemeh Darvizeh 0000-0002-3735-0472; Davide Tore 0000-0002-5087-5740; Gianluca Pontone 0000-0002-1339-6679; Riccardo Faletti 0000-0002-8865-8637.

Author contributions: Gatti M was involved in conception and design of the study; Gatti M, D'Angelo T, Dell'Aversana S, Muscogiuri G, Andreis A, Carisio A and Tore D were involved in literature review, analysis and writing of the original draft; Darvizeh F was involved in writing of the original draft; Pontone G took part in supervision of the study; Faletti R took part in supervision of the study and is the guarantor of the study; All authors worked together to editing, reviewing and final approval of article.

Conflict-of-interest statement: All authors have declared no conflicts of interest.

Country/Territory of origin: Italy

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer

Marco Gatti, Andrea Carisio, Davide Tore, Riccardo Faletti, Radiology Unit, Department of Surgical Sciences, University of Turin, Turin 10126, Italy

Tommaso D'Angelo, Department of Biomedical Sciences and Morphological and Functional Imaging, "G. Martino" University Hospital Messina, Messina 98100, Italy

Giuseppe Muscogiuri, Department of Radiology, IRCCS Istituto Auxologico Italiano, San Luca Hospital, Milan 20149, Italy

Serena Dell'aversana, Department of Radiology, S. Maria Delle Grazie Hospital, Pozzuoli 80078, Italy

Alessandro Andreis, Department of Medical Sciences, University of Turin, Turin 10126, Italy

Fatemeh Darvizeh, School of Medicine, Vita-Salute San Raffaele University, Milan 20121, Italy

Gianluca Pontone, Department of Cardiovascular Imaging, Centro Cardiologico Monzino, IRCCS, Milan 20138, Italy

Corresponding author: Marco Gatti, MD, Research Fellow, Radiology Unit, Department of Surgical Sciences, University of Turin, Via Genova 3, Turin 10126, Italy.
marcogatti17@gmail.com

Abstract

Cardiac masses diagnosis and treatment are a true challenge, although they are infrequently encountered in clinical practice. They encompass a broad set of lesions that include neoplastic (primary and secondary), non-neoplastic masses and pseudomasses. The clinical presentation of cardiac tumors is highly variable and depends on several factors such as size, location, relation with other structures and mobility. The presumptive diagnosis is made based on a preliminary non-invasive diagnostic work-up due to technical difficulties and risks associated with biopsy, which is still the diagnostic gold standard. The findings should always be interpreted in the clinical context to avoid misdiagnosis, particularly in specific conditions (*e.g.*, infective endocarditis or thrombi). The modern multi-modality imaging techniques has a key role not only for the initial assessment and differential diagnosis but also for management and surveillance of the cardiac masses. Cardiovascular magnetic resonance (CMR) allows an optimal non-invasive localization of the lesion, providing multiplanar information on its relation to surrounding structures. Moreover, with the additional feature of tissue characterization, CMR can be highly effective to distinguish pseudomasses

reviewed

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 18, 2021
Peer-review started: March 18, 2021
First decision: July 8, 2021
Revised: July 19, 2021
Accepted: October 27, 2021
Article in press: October 27, 2021
Published online: November 26, 2021

P-Reviewer: Gokce E
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

from masses, as well as benign from malignant lesions, with further differential diagnosis of the latter. Although histopathological assessment is important to make a definitive diagnosis, CMR plays a key role in the diagnosis of suspected cardiac masses with a great impact on patient management. This literature review aims to provide a comprehensive overview of cardiac masses, from clinical and imaging protocol to pathological findings.

Key Words: Cine magnetic resonance imaging; Multiparametric magnetic resonance imaging; Heart neoplasm; Multimodal imaging; Late-gadolinium enhancement; Early gadolinium enhancement

Core Tip: Cardiovascular magnetic resonance (CMR) allows an optimal non-invasive localization of cardiac masses by providing multiplanar information on its relation to the surrounding structures. Moreover, CMR can be highly effective to distinguish pseudomasses from masses as well as benign from malignant masses. Although histopathological assessment sometimes has an important role to make a definitive diagnosis, CMR is a key modality in the diagnosis of suspected cardiac masses with a great impact on patient management.

Citation: Gatti M, D'Angelo T, Muscogiuri G, Dell'aversana S, Andreis A, Carisio A, Darvizeh F, Tore D, Pontone G, Faletti R. Cardiovascular magnetic resonance of cardiac tumors and masses. *World J Cardiol* 2021; 13(11): 628-649
URL: https://www.wjgnet.com/1949-8462/full/v13/i11/628.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i11.628

INTRODUCTION

Cardiac masses diagnosis and treatment are a true challenge, although they are infrequently encountered in clinical practice[1]. They encompass a broad set of lesions that include both neoplastic (primary and secondary) and non-neoplastic masses (*e.g.*, thrombi, vegetations, pericardial cysts, mitral annulus calcification or caseous necrosis) and pseudomasses (*e.g.*, lipomatous hypertrophy of the atrial septum, coumadin ridge, Chiari network, Eustachian valve, crista terminalis)[2].

Some of those may be considered as anatomical variants, while some others represent variable prognosis; hence an accurate and early diagnosis is required to allow subsequent assessment of treatment strategy.

The most frequent cardiac masses are non-neoplastic or pseudomasses, which are potentially mimicking cardiac tumors. Cardiac thrombi have a prevalence ranging from 2%-7% in patients with atrial fibrillation or left ventricular dysfunction, while infective endocarditis may be found in 0.8%-3% intensive care unit patients[3-5]. Cardiac tumors are rarer (0.15% prevalence in echocardiographic studies) and mostly benign (90% of surgically-removed masses)[6,7]. Cardiac myxoma is the most frequent benign tumor in adults, while rhabdomyoma and fibroma are the most common in children[8]. However, malignant tumors have been reported to be at least 20 times more common in autopsy studies (1.23%)[9,10]. Sarcomas are the most common primary malignant tumors[11]. Among secondary tumors, the most frequently associated extracardiac neoplasms are lung, lymphoma, breast and esophageal cancer [12].

The clinical presentation of cardiac tumors is highly variable and depends on several factors such as size, location, relation to other surrounding structures and mobility[13]. As a consequence, symptoms may range from incidental detection through routine imaging tests in asymptomatic to exertional dyspnea, cardiogenic shock or sudden cardiac death[10]. Signs and symptoms may be non-specific, such as fever and weight loss, or associated with distal embolization of tumor (stroke or peripheral embolization in case of left-sided mass, pulmonary embolism in case of right-sided mass) or due to direct mass effects (obstruction, coronary artery encasement, pericardial effusion with cardiac tamponade, arrhythmia)[14].

Due to technical difficulties and risks associated with biopsy, which is still the diagnostic gold standard, the presumptive diagnosis is based on a preliminary non-invasive diagnostic work-up[10]. The clinical context should always be considered for the diagnostic work-up, particularly in specific conditions (*e.g.*, infective endocarditis or thrombi). The modern multi-modality imaging techniques have a key role not only for the primary assessment and differential diagnosis but also for management and surveillance of the cardiac masses[15]. Among different techniques, two dimensional-echocardiography is the first level diagnostic test, due to its wide availability and low costs[16]. However, echocardiography may be inconclusive due to limited information about the composition of cardiac mass or pericardial/ myocardial infiltration, limited field of view and variable quality of acoustic window[17].

Cardiovascular magnetic resonance (CMR) is an advanced and highly accurate imaging test capable of providing not only accurate tissue characterization of the mass but also multiplanar information on its relation to surrounding structures, with a higher spatial resolution. Perfusion sequences are useful in the assessment of mass vascularization, while early- (EGE) and late-gadolinium enhancement (LGE) sequences are essential to detect the presence of thrombi and to provide further characterization of the mass[18,19]. Indeed CMR may provide reliable information for the differentiation of malignant from benign tumors[20,21].

This review aims to provide a comprehensive overview of cardiac masses, from exam protocol to pathological findings.

CMR PROTOCOL

A CMR protocol for the study of a suspected cardiac mass should encompass all available sequences for tissue characterization in order to distinguish pseudomasses from cardiac masses (non-neoplastic and neoplastic)[22].

A CMR exam for a suspected cardiac mass can be divided in two parts: The mass localization and its tissue characterization.

The exam should start with an axial steady-state free precession (SSFP) with a balanced T1/T2 effect sequences covering the entire thorax. After that cine-SSFP imaging in long and short axis planes should be performed in order to identify correctly the mass and an additional stack in at least two orthogonal customized imaging planes should be performed to confirm the presence, the location and the extension of the mass (*i.e.* intracavitary, intracardiac or extracardiac). Moreover cine-SSFP sequences allow the assessment of the mass mobility and its attachment points and the hemodynamic impact on cardiac valves[23]. In case of valve involvement, phase-contrast sequences might be performed for quantitative assessment of the hemodynamic effect of the mass[24].

The next step is tissue characterization utilizing all available sequences. "Black-blood" images may also be used to localize a suspected cardiac mass and to provide some information about its tissue composition. Such sequences are generally acquired using a double-inversion recovery fast spin-echo sequence with an initial non slice-selective 180° inversion pulse followed by a slice-selective 180° pulse; a third slice-selective 180° inversion pulse (triple inversion recovery) can be added to obtain fat saturation, resulting in low intensity of fat containing lesions[25,26].

In particular morphologic T1-weighted and T2-weighted, followed by fat-suppressed imaging, should be performed before contrast administration in the same optimal imaging planes identified as above.

Novel T1 and T2 quantitative mapping can provide quantitative information on the studied mass. T1 mapping should be performed before and after the injection of contrast medium to evaluate T1 native, T1 enhanced and extracellular volume[27,28].

A cardiac mass protocol must include contrast-enhanced imaging with first pass perfusion sequences, EGE images, repetition of T1-weighted sequences and LGE sequences.

Perfusion imaging and EGE sequences are used to evaluate the lesion vascularization, the presence of hyperemia near the lesion and for differential diagnosis with thrombus. EGE images are acquired about 3 min after gadolinium injection.

LGE sequences are performed 10-15 min after contrast injection. LGE sequences are fast (or turbo) gradient echo inversion recovery sequences (IR-fast spin-echo)[22,24,29]. The inversion recovery pulse is used to null the signal of normal myocardium in order to maximize the contrast of areas with gadolinium accumulation (edema, increased extracellular space, necrosis). It is crucial to select a proper inversion time (TI). These sequences should be acquired in short axis covering all the ventricles and in

the optimal imaging planes mentioned above both for tissue characterization of the mass and identification of any underlying cardiac pathology.

In summary, to assess each suspected cardiac mass, the protocol must be tailored in terms of the optimal acquisition planes and sequences in order to obtain an accurate tissue characterization.

Table 1 summarizes CMR characteristics of cardiac masses (non-neoplastic and neoplastic).

PSEUDOMASS

Eustachian valve

The eustachian valve, also known as the valve of the inferior vena cava (IVC), is a thin flap-like structure located in the right atrium (RA) at the orifice of IVC that helps direct blood flow through the foramen ovale during embryogenesis. Note that the terms eustachian ridge and eustachian valve are occasionally used interchangeably. However, the eustachian ridge technically refers to the fibrous structure contiguous with the free margin of the eustachian valve[30]. When in doubt, CMR imaging is particularly useful for characterization of the lesion on the basis of its typical location at the inferior cavoatrial junction, lack of enhancement and linear shape.

Crista terminalis

Crista terminalis, or terminal crest, is a horseshoe or twisted C-shaped fibromuscular ridge in the RA. It originates from the atrial septum, extends anteriorly, goes toward the right of the superior vena cava (SVC) orifice, subsequently descends along the posterolateral wall of the RA and turns anteriorly, terminating to the right of the IVC orifice. It is the remnant tissue from the septum spurium, which divides the embryologic primitive RA and sinus venosus[31]. It is an important anatomical landmark in electrophysiology owing to its relation to the sinoatrial node and artery, which should not be injured. Crista terminalis is present in every heart but is not always visualized at imaging. It varies in size, typically 3–6 mm, and is more prominent superiorly. Thrombus is a differential diagnosis (Figure 1), especially in patients with an indwelling right atrial catheter.

Warfarin ridge (coumadin ridge)

The coumadin ridge has been described from echocardiographic studies as a ridge of atrial tissue separating the left atrial appendage (LAA) from the left upper pulmonary vein[32]. It can present as a linear structure or even sometimes as a nodular mass that protrudes into the left atrium (LA). In the past, this structure was often mistaken for thrombus and resulted in patient being prescribed anticoagulation therapy with warfarin (coumadin), from which it derives its name. On cine-SSFP sequences, a prominent coumadin ridge can be identified by its typical location in the roof of the LA adjacent to the left upper pulmonary vein; a particularly prominent ridge can appear as a dark "mass" protruding into the bright left atrial cavity (Figure 2). Thrombus and myxoma are differential diagnosis. As the coumadin ridge is normal cardiac tissue, it should have the same signal intensity as adjacent myocardial tissue on both T1 and T2 -weighted imaging and typically does not show late gadolinium enhancement.

Lipomatous hypertrophy of the interatrial septum

Lipomatous hypertrophy of the interatrial septum (IAS) is a benign condition characterized by mass like deposition of brown fat in the IAS. It results from adipose-cell hyperplasia and has been linked to advanced age and obesity[33]. Classically, there is sparing of the fossa ovalis, resulting in a dumbbell shape of the IAS. Unlike cardiac lipoma, lipomatous hypertrophy of the IAS appears as thickening and is not encapsulated. Lipoma is a differential diagnosis. Fat-suppressed sequences can be used at CMR imaging to characterize this pseudo-lesion; unenhanced chest CT can also help in confirmation of the diagnosis by measuring fat attenuation and demonstrating the dumbbell shape (Figure 3).

Table 1 Cardiovascular magnetic resonance characteristic (location, signal intensity and contrast contrast-enhanced relative to that of adjacent normal myocardium) of benign and malignant cardiac masses

Lesion	Location	T1-WI	T2-WI	Cine-SSFP	Perfusion	EGE	LGE
Non-neoplastic							
Thrombus Acute/subacute	Mural or intraluminal	Iso-Hyper	Iso-Hyper	Iso-hypo	No enhancement	No enhancement	Hypointense border and brighter central zone
Thrombus Chronic	Mural or intraluminal	Hypo	Hypo	Iso-hypo	Rare	No enhancement	Rarely heterogeneous
Pericardial cyst	Right cardiophrenic angle	Hypo	Hyper	Hyper	No enhancement	No enhancement	No enhancement
Mitral annular calcification	Annular fibrous ring of the left atrio-ventricular valve	Hypo	Hypo	Iso-hypo	No enhancement	Peripheral rim of enhancement	Peripheral rim of enhancement
Liquefaction necrosis	Annular fibrous ring of the left atrio-ventricular valve	Mildly Hyper	Mildly Hyper	Iso-hypo	No enhancement	Peripheral rim of enhancement	Peripheral rim of enhancement +/- core enhancement
Neoplastic - Benign							
Myxoma	Left atrium, arising from the interatrial septum	Iso (heterogeneous)	Hyper (heterogeneous)	Hypo	Heterogeneous	Heterogeneous	Heterogeneous
Papillary fibroelastoma	Atrial side of the mitral valve and the aortic surface of the aortic valve leaflet	Iso	Iso	Hypo	Usually not assessable	Mild and homogeneous or no enhancement	Homogeneous or no enhancement
Lipoma	Atrial septum and epicardium, but it may occur anywhere in the heart	Hyper	Hyper (Hypo on STIR images)	Hyper (with black boundary artifact or India ink artifact)	No enhancement	No enhancement	No enhancement
Hemangioma	Every cardiac chamber and also from pericardial space	Iso	Hyper	Hyper	Heterogeneous, intense and prolonged	Homogeneous or heterogeneous	Homogeneous or heterogeneous
Fibroma	Intramural growth in the ventricles (interventricular septum or the ventricular free wall)	Iso	Hypo	Iso-hypo	Mild and homogeneous	Mild and homogeneous	No enhancement or minimal uptake
Rhabdomyoma	Intramyocardial or intracavitary, with intraventricular growth that may cause outflow obstruction	Iso	Mildly Hyper	Iso-hypo	No enhancement or minimal uptake	No enhancement or minimal uptake	No enhancement or minimal uptake
Cardiac teratomas	Intrapericardial (usually compressing superior vena cava and/or right atrium)	Iso or Hypo	Hyper	Iso or Slightly hyper	No enhancement	Mild and heterogeneous	Heterogeneous
Paraganglioma	On the roof of left atrium	Iso-Hypo with "salt and pepper" appearance	Hyper with "salt and pepper" appearance	Hyper	Strong enhancement	Heterogeneous Peripheral	Heterogeneous Peripheral
Neoplastic - malignant: Primary							

cardiac tumor							
Angiosarcoma	Right atrium close to atrio-ventricular sulcus	Iso-Hyper (heterogeneous)	Hyper (heterogeneous)	Iso (heterogeneous)	Strong enhancement	Marked and Heterogeneous	Marked and Heterogeneous
Leiomyosarcoma	Typically involve the left atrium	Iso	Iso-Hyper	Iso	Heterogeneous, intense	Marked and Heterogeneous	Marked and Heterogeneous
Rhabdomyosarcoma	Multiple masses and there is not any predilection in terms of cardiac structures involved	Iso	Iso-Hyper (hyper on STIR images)	Iso	Heterogeneous, intense	Marked and Heterogeneous	Marked and Heterogeneous
Lymphoma	Right chambers, often right ventricle and are associated with pericardial effusion	Hypo-Iso	Mildly Hyper (more evident on STIR images)	Iso	Mild	Heterogeneous	No or progressive mild heterogeneous enhancement
Mesothelioma	Pericardium	Iso	Hyper (heterogeneous)	Iso	Progressive enhancement	Intense enhancement	Intense enhancement
Malignant - Malignant: metastatic disease	Mainly involve myocardium and pericardium	Low (except for Melanoma which is Hyper)	Hyper	Iso	Heterogeneous	Heterogeneous	Heterogeneous

T1-WI: T1-weighted images; T2-WI: T2-weighted images; STIR: Short tau inversion recovery; Cine-SSFP: Cine-steady state free precession; EGE: Early gadolinium enhancement; LGE: Late gadolinium enhancement; Hypo: Hypointense; Iso: Isointense; Hyper: Hyperintense.

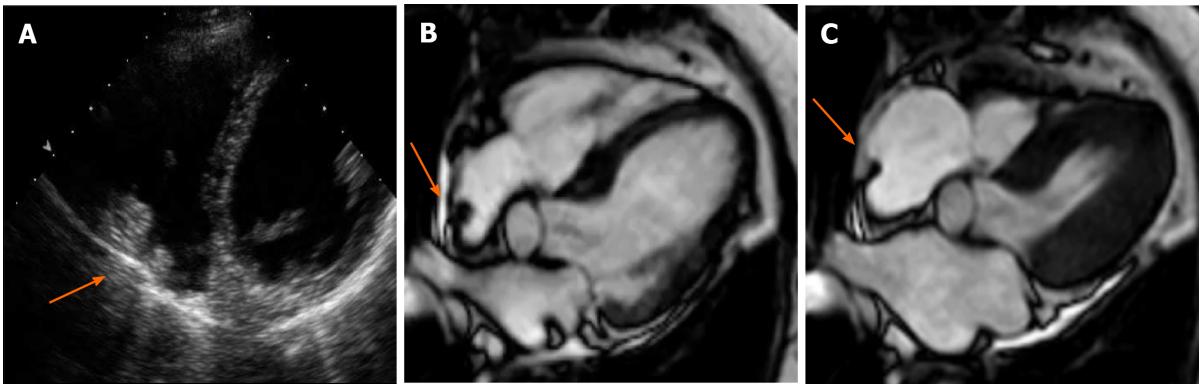

Figure 1 Cardiac mass in a 68-year-old male. Transthoracic echocardiography shows (A) an apparently free mass in the right atrium mimicking a thrombus or a tumor (orange arrow). Cardiovascular magnetic resonance (B, C: 4-chamber cine steady state free precession diastolic and systolic frame respectively) reveals a pseudomass: A hypertrophied crista terminalis (orange arrow) with appearance of right atrial mass on transthoracic echocardiography.

MASS - NON-NEOPLASTIC

Thrombus

Intracardiac thrombi represent the most common cardiac masses, with a prevalence ranging between 2%-25% in normal population and between 3%-50% in patients with atrial fibrillation or left ventricular systolic dysfunction[3,34].

In case of atrial dilation or fibrillation, thrombi are usually located in the posterior wall of the LA or in the LAA. In the left ventricle, the location of thrombi usually relates to presence of regional or global wall motion abnormalities, as seen after myocardial infarction or in cardiomyopathies[35]. When thrombi are found in patients with normal systolic function and contractility, the presence of coagulation disorders should be considered[36]. Occasionally, thrombi can be located in the RA or in vena cava, especially in patients with enlarged right chambers and with central venous lines, and can mimic other masses[37-39].

Identification of a cardiac thrombus is pivotal to start anticoagulation treatment and to prevent systemic or pulmonary embolic events[40]. In most cases, the diagnosis is accidental, and patients are asymptomatic. Generally, thrombi are attached to cardiac walls by a broad base and are immobile. If they are pedunculated and mobile, distin-

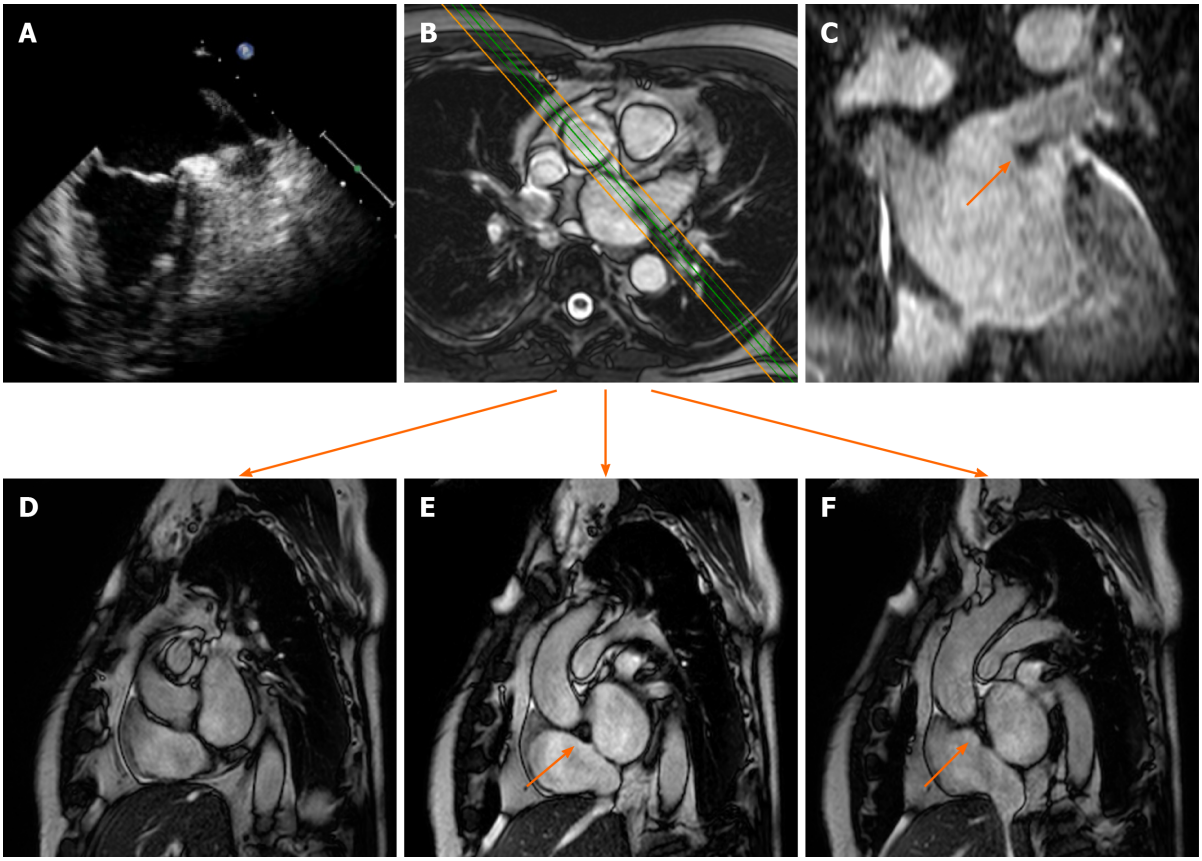

Figure 2 Cardiac mass in a 63-year-old male with atrial fibrillation. Transthoracic echocardiography shows (A) a nodular mass that protrudes into the left atrium at the inlet of the left appendage. The patient underwent 2 mo of oral anticoagulant therapy, and the "mass" did not change. It was therefore requested a cardiovascular magnetic resonance (CMR) (B: axial cine- steady state free precession (SSFP) with the correspondent perpendicular plane oriented according to the green and orange lines and reported in D, E and F), moreover it was performed a three dimensional-steady state free precession SSFP acquisition with an oriented reconstruction (C). Overall the CMR shows the presence of pseudomass (orange arrow), a prominent coumadin ridge in the roof of the left atrium adjacent to the left upper pulmonary vein.

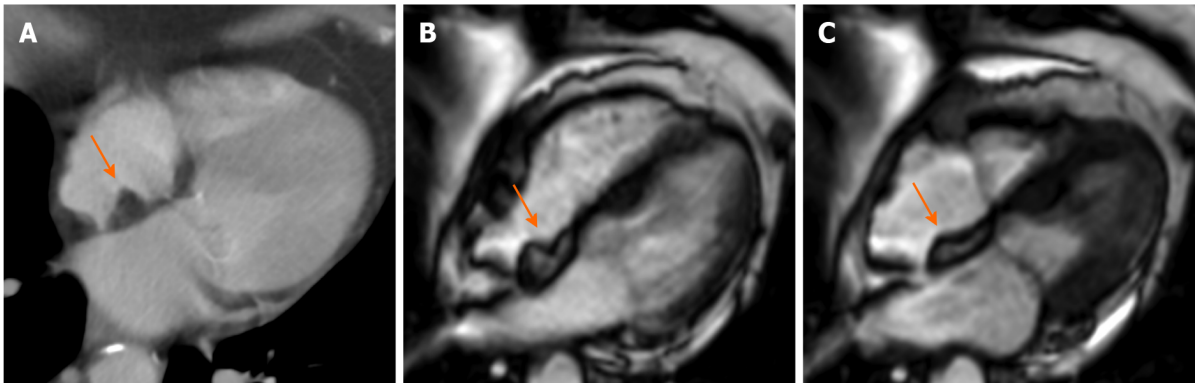

Figure 3 Sixty-five-year-old male patient with a dumbbell-shaped mass along the interatrial septum with negative Hounsfield Unit values on computed tomography scan (A), cardiovascular magnetic resonance cine-steady state free precession images (B and C, diastolic and systolic frame respectively) reveals the chemical shift artifact, also known as "India ink" artifact, typical of structures with adipose content. These findings are in keeping with lipomatous hypertrophy of the interatrial septum (orange arrow).

guishing them from other tumors may be challenging.

CMR has excellent contrast resolution and allows for superior soft tissue characterization. It provides a combined evaluation of morphology, composition and LGE of cardiac masses, with unique advantage of being non-invasive assessment[41,42].

On CMR, thrombi may have different signals, depending on their age and sequence used. Fresh thrombi have a higher signal than myocardium on T1-weighted sequences, and contrast is further accentuated on T2-weighted images, due to high amount of

hemoglobin[35]. After 1-2 wk, they tend to have increased signal on T1-weighted images and decreased on T2-weighted images, due to paramagnetic effect caused by deoxyhemoglobin and methemoglobin in the organizing thrombus[38]. Chronic organized thrombi have low signal either on T1- and T2-sequences, due to loss of water and protons, and they can appear heterogeneous in presence of calcifications (Figure 4).

Differentiation between thrombus and slow-flowing blood on spin-echo sequences may be difficult, due to poor contrast. On the other hand, gradient-echo sequences (or bright-blood imaging) allow for an improved contrast of thrombi from the surrounding blood pool, and clots usually have lower signal compared to normal myocardium[38].

The differentiation between thrombus and myocardium on bright-blood imaging can be difficult when thrombi have similar signal intensity of adjacent myocardium. However, the advantage of bright-blood imaging is represented by cine-CMR, which provides a dynamic evaluation of cardiac motion and blood flow. Balanced SSFP sequences are the most used for cine-CMR in clinical routine for precise detection of mural thrombi[43]. Other sequences that have been successfully used to detect thrombi are phase-contrast sequences with myocardial tagging. Mapping sequences do not provide any T1 or T2 values useful for diagnosis. However, a characteristic pattern of hyperintensity-isointensity-hypointensity has been described for thrombi when TI scout is performed at increasing inversion times, and it may allow to differentiate clots from other cardiac tumors[42].

The method that has shown the best performance for thrombus imaging on CMR is represented by LGE imaging[4]. This technique allows for a straightforward diagnosis, even in case of small thrombi, and independently of their location. Moreover, the presence of thrombus enhancement may also help to differentiate between subacute and chronic clots. In fact, subacute thrombi present homogeneously low-signal, without late enhancement, and can manifest magnetic susceptibility artifacts. In contrast, organized thrombi have intermediate signal and can be heterogeneous due to multiple areas of late enhancement, hindering a prompt differentiation from other cardiac masses[44].

Pericardial cyst

Pericardial cysts account for approximately 7% of all mediastinal masses and 33% of all mediastinal cysts, with an incidence of 1/100000. They are mostly congenital lesions, and commonly located in the right (51%–70%) or left cardiophrenic angles (28%–38%)[45-47]. The cyst walls consist of a single layer of mesothelial cells, and they are usually filled with clear fluid. On CMR they have low signal on T1-weighted sequences and high signal on T2-weighted images[48,49]. There is not fluid enhancement on LGE imaging, but enhancing walls or intracystic septations may be observed (Figure 5). CMR ability to discriminate these lesions from other mediastinal masses allows to avoid further invasive diagnostic procedures, since most patients are usually asymptomatic.

Symptoms may occur when cysts impinge upon or erodes into adjacent structures. In case of cardiac compression, patients may present with retrosternal pain or congestive heart failure symptoms, especially if the right side of the heart is involved. Treatment is usually conservative and CMR is particularly helpful to assess stability of the lesion. When pericardial cysts do not enlarge and patients are asymptomatic, a continued surveillance is the favored option. In contrast, when cysts enlarge and patients present symptoms, surgery may be indicated, mainly to prevent compressive effects and life-threatening complications[50].

Mitral annular calcification and liquefaction necrosis

Calcification of the mitral annulus is the result of a chronic non-inflammatory process, which is characterized by calcium deposition in the annular fibrous ring of the left atrio-ventricular valve[51].

It is more frequent in older patients, and it is related to altered metabolism of calcium phosphate and to chronic renal disease. Mitral annular calcification may present as an immobile mass, generally located in the inferior or inferolateral portion of the mitral anulus. In severe cases it may involve the whole annulus and compress the adjacent myocardium. Usually, it is composed by a calcified core enclosed by a fibrotic envelope. On CMR, it is typically characterized by low signal on T1- and T2-weighted sequences, without enhancement after intravenous injection of gadolinium. However, the fibrotic envelope may show a peripheral rim of enhancement on LGE imaging[51] (Figure 6). Rarely, this lesion can evolve to liquefaction necrosis (or caseous calcification). In this case, the core contains a mixture of cholesterol, fatty

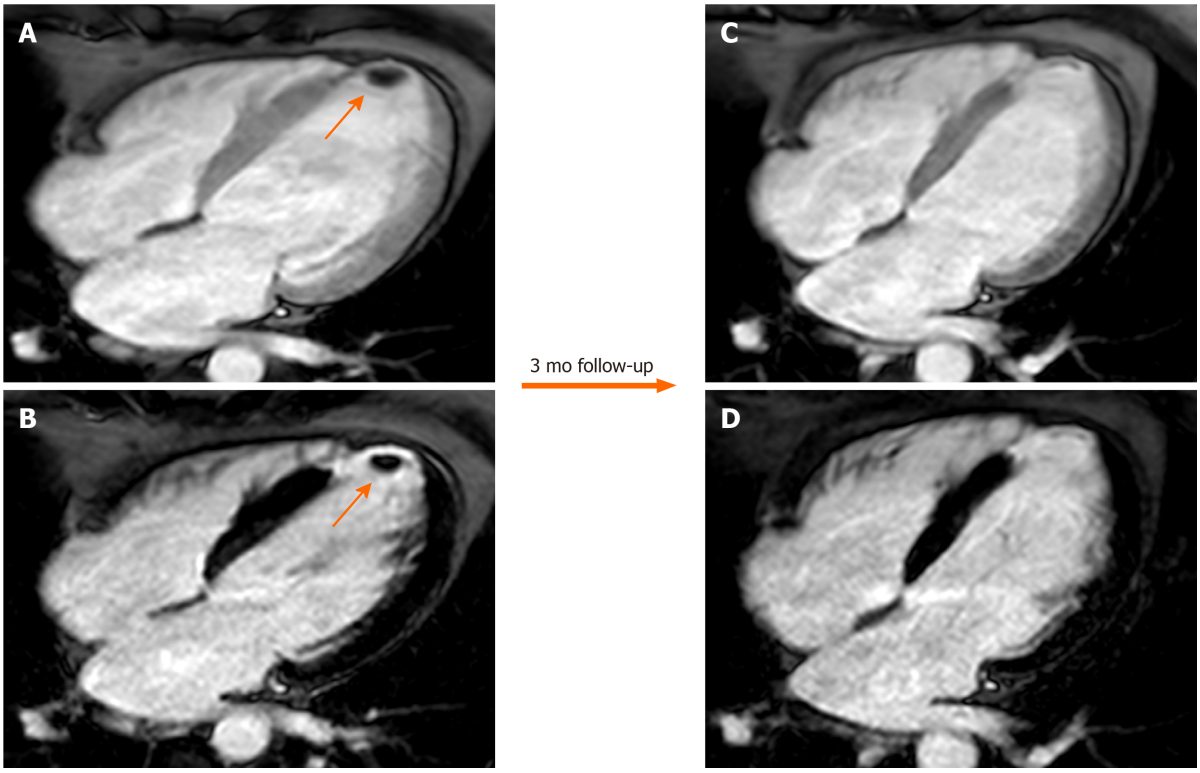

Figure 4 Sixty-six-year-old male patient with a history of myocardial infarction and suspected thrombotic formation at echocardiographic transthoracic examination. Cardiovascular magnetic resonance shows a hypointense intraventricular "mass" at the left ventricular apex (orange arrow) in the early gadolinium enhancement (A) and late gadolinium enhancement (LGE) (B) sequences near the infarcted wall (*i.e.* with transmural LGE involvement). The patient underwent 3 mo of anticoagulant therapy with disappearance of the thrombus in the follow-up examination.

acids, and amorphous eosinophilic infiltrate, with a surrounding rim that encloses macrophages, lymphocytes and multiple necrotic areas with calcifications[29].

In contrast to the previous entity, the proteinaceous and fatty components of the central part of the lesion may manifest with high signal on T1- and T2-weighted sequences. Moreover, core enhancement is typically observed, either in the early or late phases after gadolinium injection[29]. Both these entities are considered benign and they are usually asymptomatic and discovered as incidental findings. Symptoms are usually caused by related complications such as mitral stenosis or regurgitation, infective endocarditis and embolization.

Vegetations

CMR can be of help in visualization of valve or mural vegetations, either to clarify echocardiographic findings or to establish the diagnosis. They may not be visible on dark-blood imaging, while they are better depicted on cine-CMR, manifesting as low-signal areas that follow the motion of the cusp to which they are connected[52]. The differentiation from thrombus may be difficult, because both masses usually do not show contrast enhancement. However, a peripheral rim enhancement on LGE imaging has been observed in vegetations and might facilitate the differentiation from other cardiac masses. The presence of adjacent myocardial enhancement or endothelial lining may indicate irreversible myocardial damage or fibrosis, and they may represent indirect signs of infective endocarditis or perivalvular abscess[53].

Cardiac vegetations can also be found secondary to inflammation, in association with sterile endocarditis, as Libman-Sacks endocarditis. This is characteristic of patients suffering from systemic lupus erythematosus and can manifest with small verrucous vegetations, more frequently involving the mitral and aortic valves[54].

NEOPLASTIC-BENIGN

Myxoma

Cardiac myxomas, the most common primary benign cardiac tumor, are well-defined

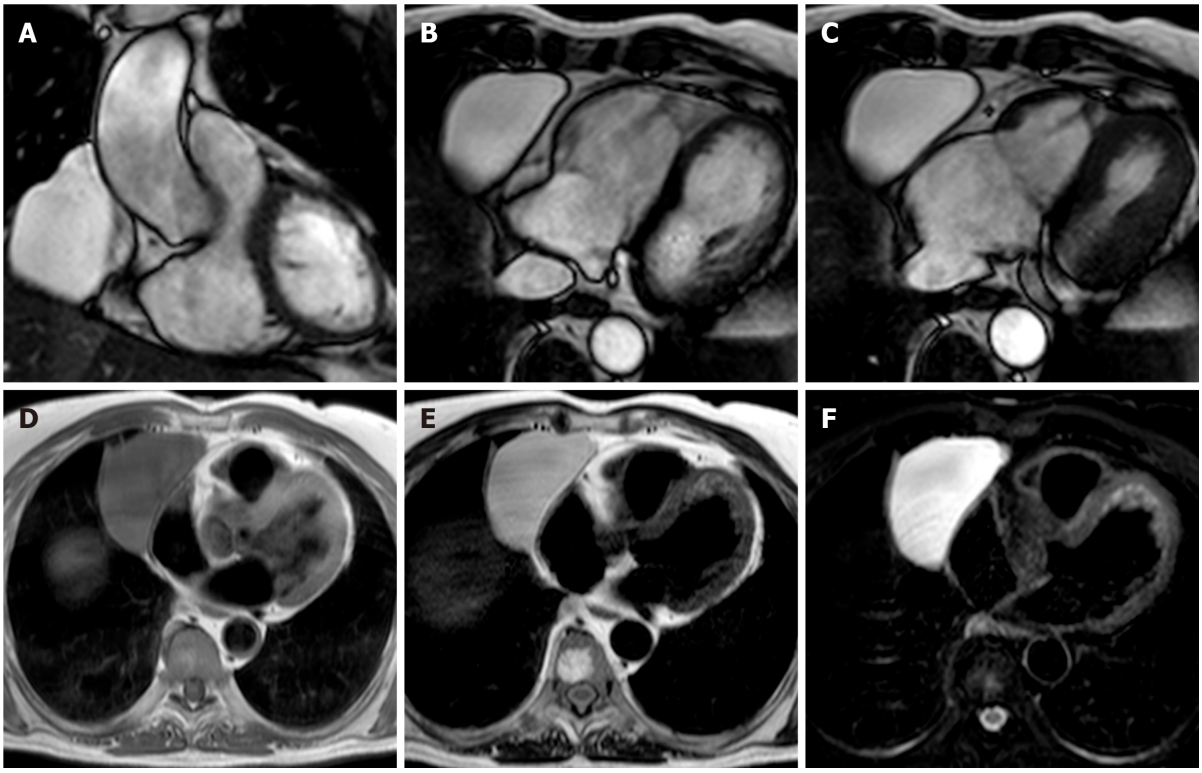

Figure 5 Fifty-seven-year-old female patient with parenchymal mass in the right cardiophrenic angle on chest X-ray. This finding was first investigated by chest computed tomography and then by cardiovascular magnetic resonance (CMR) (A-C). The CMR confirm the presence of the mass on cine-steady state free precession images (A and B, two orthogonal diastolic frames of plane through the mass respectively), without sign of infiltration confirmed by the preserved movement of the heart chambers in relation to the mass itself. The mass shows low signal on T1-weighted sequences (D) and high signal on T2-weighted images (E and F, without and with fat suppression, respectively). These findings are in keeping with pericardial cyst.

spherical or ovoidal mobile lobulated masses frequently in the LA (80%), arising from the IAS (80%)[55,56]. Less common locations are the posterior and lateral LA wall, the LAA, the mitral and tricuspid valve, the posterior RA wall and, rarely, the ventricles and the pulmonary artery[57]. The endocardial attachment point may be broad, sessile or narrow or pedunculated (typically mobile). Myxomas prolapse through the mitral valve has been reported in 30% of cases. Cardiac myxoma may be part of the Carney complex[58].

There are three patterns on CMR: Most frequently it is isointense in T1-weighted and hyperintense in T2-weighted images. Conversely, it might appear hypointense in both T1 and T2 due to calcifications or extremely hyperintense in T2 with "pseudo-cystic" appearance[56,57]. At first pass perfusion, it presents weaker enhancement than myocardium (16%-66%)[55]. About half of cardiac myxomas present heterogeneous LGE[23,57] (Figure 7). On parametric imaging, they show elevated native T1 and T2 relaxation times and extracellular volume values[27].

Papillary fibroelastoma

Papillary fibroelastoma (PF) is the most common cardiac valve tumor. It can arise from any endocardial surface but the most common locations are the atrial side of the mitral valve and the aortic surface of the aortic valve leaflets[23]. PFs are usually small lesions (< 1.5 cm) composed of collagen and elastic fibers lined by endothelium with a short pedicle[59]. PF presents signal isointense to normal myocardium in both T1- and T2-weighted images. On SSFP sequences, it appears as a well circumscribed mobile valve nodule with possible perilesional artefact[60]. PFs may have homogeneous LGE [61] (Figure 8). PFs have elevated native T1 and T2 relaxation times[23].

Lipoma

Lipoma is the second most common benign cardiac tumor; most frequently it grows within the atrial septum and epicardium, but it may occur anywhere in the heart.

At CMR lipoma generally shows a homogeneous nodular elevated signal intensity on T1-weighted sequences, slightly hyperintense on T2-weighted images and hypointense on fat-saturated images. Lipomas do not present contrast enhancement or

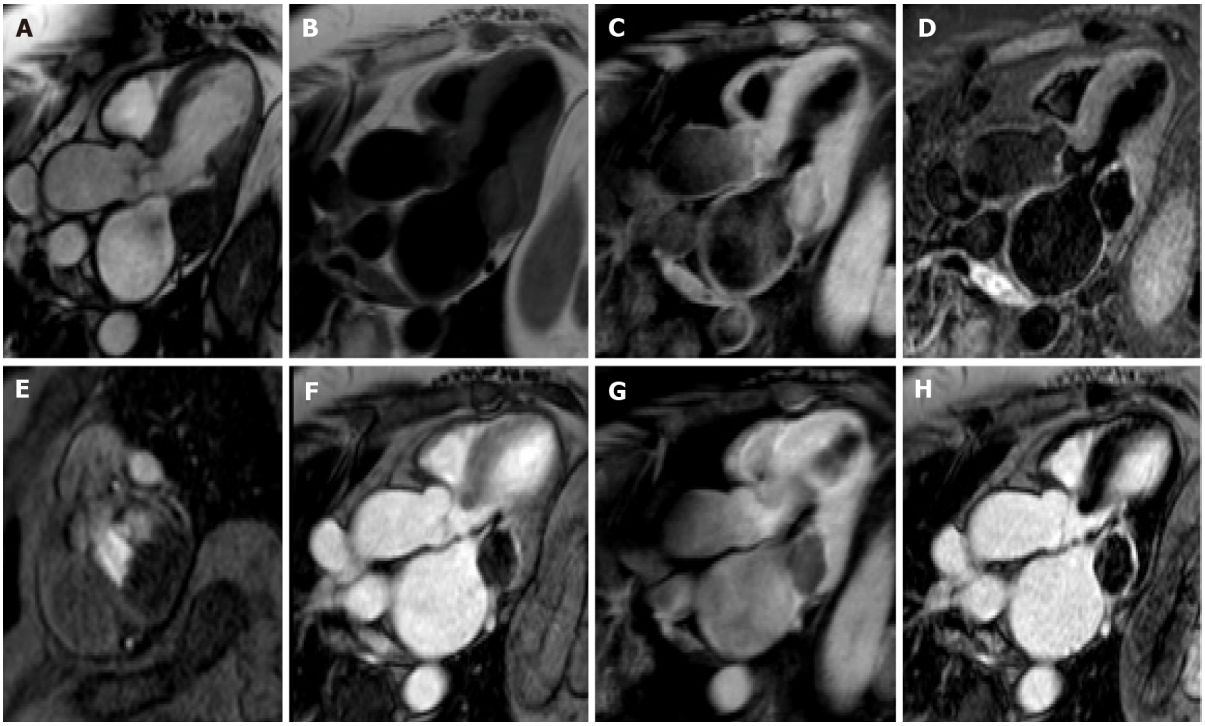

Figure 6 Eighty-year-old female with hyperechoic mass of uncertain significance in the left atrio-ventricular groove discovered at transthoracic echocardiography. Cardiovascular magnetic resonance confirms the presence of the mass with the cine- steady state free precession images (A). The mass shows slight hyperintense signal on T1-weighted images without and with fat suppression (B and C, respectively), due to the presence of proteinaceous material, and hypointense signal on short tau inversion recovery images (D). The mass shows no contrast uptake during perfusion sequences (E) and no contrast enhancement both on early gadolinium enhancement images (F), T1- weighted images (G) repeated after the contrast medium injection, and late gadolinium enhancement images (H) with a peripheral rim of enhancement. These findings are in keeping with caseous calcification of the mitral valve.

LGE (Figure 9). They have elevated T1 relaxation times with intermediate values on T2 mapping[23,62].

Hemangioma

Hemangioma accounts for approximately 5%-10% of benign cardiac masses. They are slow flow vascular malformations that can arise in every cardiac chamber and also from pericardial space. Most patients are asymptomatic, and cardiac hemangioma is discovered serendipitously; symptomatic patients may present with dyspnea on exertion, chest pain, arrhythmias, pericarditis, pericardial effusion, syncope and sudden death. Cardiac hemangiomas can occur in Kasabach-Merritt syndrome, characterized by multiple systemic hemangiomas, recurrent thrombocytopenia and consumptive coagulopathy[63].

At CMR hemangiomas have isointense signal to myocardium on T1-weighted images because of slow blood flow and high signal intensity on T2-weighted images [23,63,64]. On first pass and LGE sequences they have intense and prolonged enhancement and may appear heterogeneous depending on the presence of fibrotic tissue and calcifications[23,64].

Fibroma

Fibromas are benign neoplasms of the connective tissue that originate from fibroblasts, predominantly seen infants and children (the second most common congenital tumor after rhabdomyoma). Almost one-third of patients with cardiac fibroma are asymptomatic and they are mostly diagnosed incidentally. Symptomatic patients may present with arrhythmias, heart failure, or sudden death. Fibromas are usually solitary tumors (unlike rhabdomyomas) usually with intramural growth that involve the ventricles, either in interventricular septum or ventricular free walls[41,65]. They do not regress, unlike rhabdomyomas, therefore surgery is required[66]. Macroscopically, they are solid tumors with dimensions varying from few millimeters to a size that can obliterate cardiac chambers. Microscopically, they are composed of fibroblasts, and calcification is a common finding[67]. At echocardiography, they appear as a large, noncontractile, heterogeneous solid mass[65]. On CMR fibroma are well-defined masses, generally isointense or hypointense on T1-weighted images, and homogen-

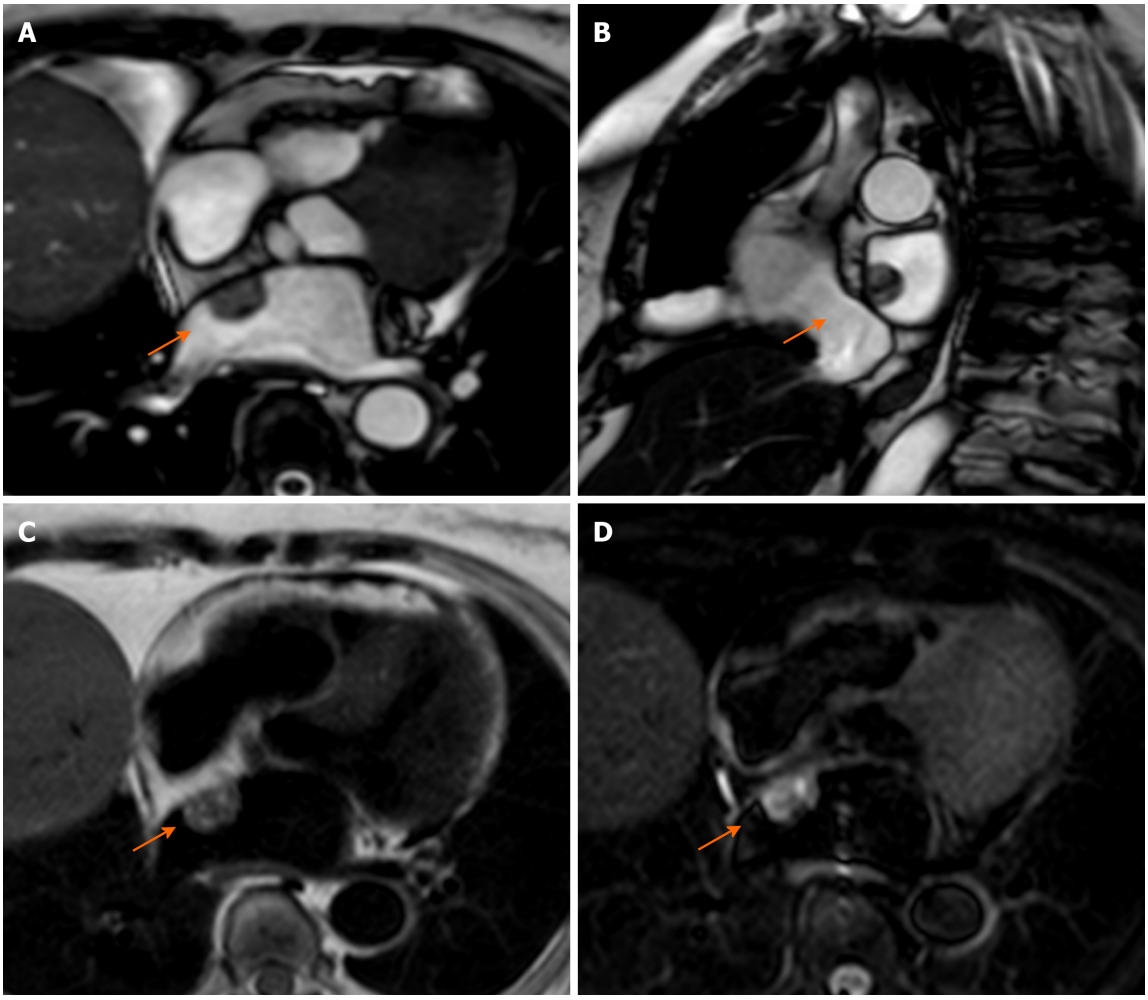

Figure 7 Seventy-nine-year-old female patient with left atrial mass adherent to the interatrial septum discovered on cardiac computed tomography angiography. The cardiovascular magnetic resonance confirms the presence of the mass using the cine- steady state free precession images (A and B, two orthogonal planes along the mass respectively). The site of lesion and its heterogeneous appearance on T2-weighet sequence (C and D) short tau inversion recovery, are in keeping with cardiac myxoma.

eously hypointense on T2-weighted images[41,65].

Fibromas can show different enhancement patterns after gadolinium administration. In fact, they may not show any LGE, or manifest homogeneous or heterogeneous enhancement with isointense rim and hypointense core, which is due to decreased blood supply from the surrounding myocardium[64] (Figure 10).

Rhabdomyoma

Rhabdomyomas are very rare in adults, while they are the most common cardiac tumors during fetal life and childhood. From a histopathological point of view, rhabdomyomas are hamartomas, and they are often associated with tuberous sclerosis. In particular, the incidence of tuberous sclerosis in patients with cardiac rhabdomyomas is 60%–80%, and more than 50% of patients with tuberous sclerosis have rhabdomyomas[65].

Rhabdomyomas are multiple in more than 60% of cases, and this multiplicity has an even higher association with tuberous sclerosis; nevertheless, findings of multiple cardiac masses at prenatal echocardiogram can be the first suggestion of tuberous sclerosis[65]. Rhabdomyomas are usually intramyocardial or intracavitary, with intraventricular growth that may cause outflow obstruction; less commonly, they may be located in the atrioventricular groove ,possibly causing arrhythmias related to an accessory pathway[65]. The majority of rhabdomyomas spontaneously regress in early childhood, therefore surgery is needed only in case of heart failure due to outflow obstruction or arrhythmias[68]. Rhabdomyomas appear as hyperechoic solid masses on echocardiogram[65]. On CMR, they are isointense (or slightly hyperintense) on T1-weighted images, and hyperintense on T2-weighted images with mild LGE[29].

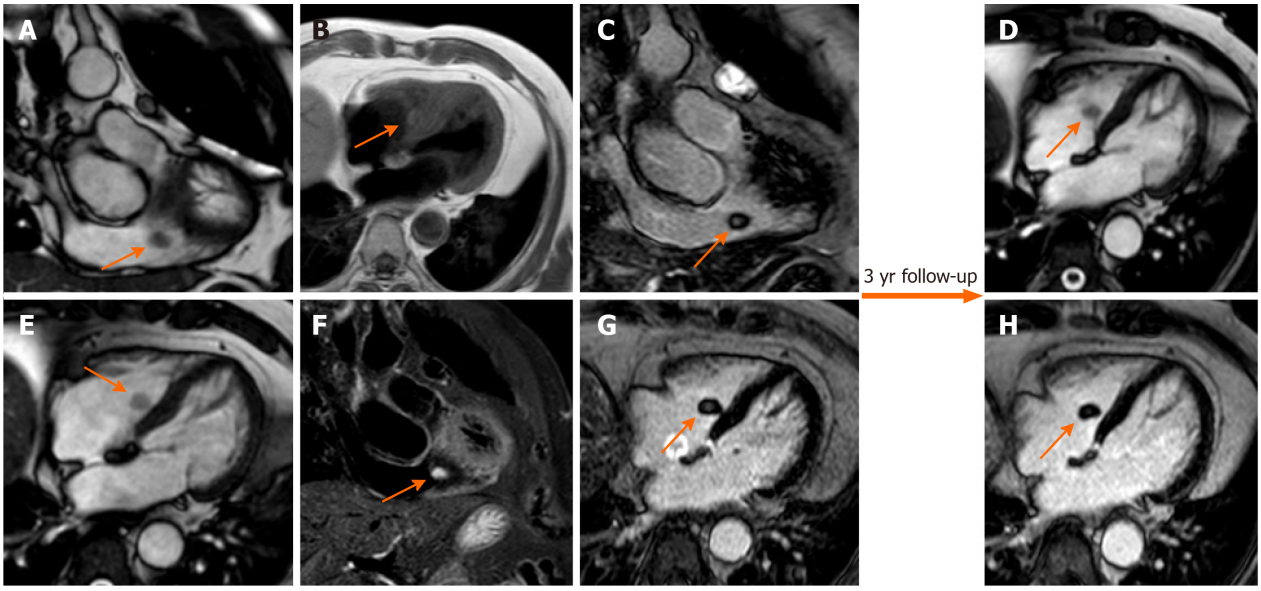

Figure 8 Seventy-one-year-old female with incidental finding of cardiac mass adherent to the septal leaflet of the tricuspid valve on cardiovascular magnetic resonance. The examination was performed for suspected noncompact myocardium on a previous ultrasound examination in a patient with known metastatic thyroid cancer. Orange arrow shows a mobile "valvular" mass at cine-steady state free precession (SSFP) imaging (A and B), with intermediate signal on T1-weighted images (C), high signal on T2 short tau inversion recovery images (D) and with poor enhancement at late gadolinium enhancement (LGE) images (E and F). This location of the mass and its cardiovascular magnetic resonance (CMR) features are in keeping with fibroelastoma. The patient underwent a periodic CMR follow-up for 3 years (G: cine-SSFP and H: LGE sequences), and the mass shows no change.

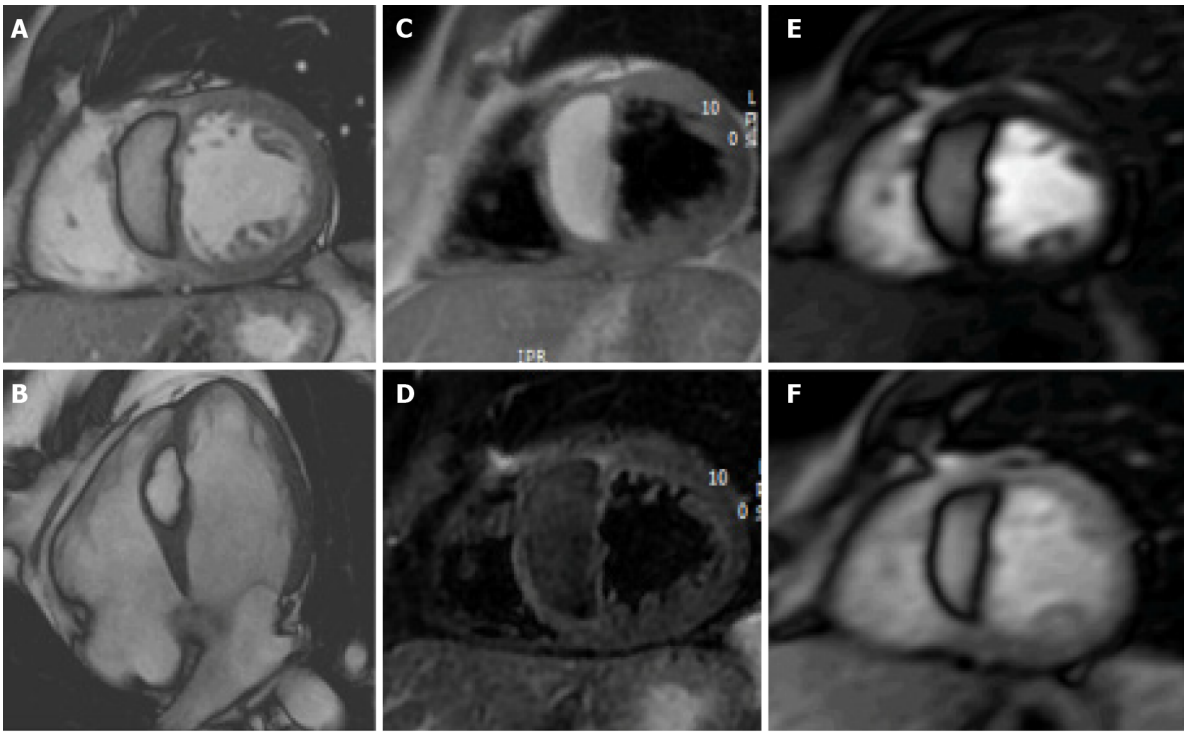

Figure 9 Fifty-one-year-old male patient, with incidental finding of a suspicious intraseptal hyperechoic mass at transesophageal echocardiography. Cine-steady state free precession magnetic resonance (A and B) confirms the presence of an intraseptal mass with a chemical shift artefact at the border. The mass shows high signal intensity on proton density-weighted images (C) and low signal intensity on short tau inversion recovery images (D). The mass shows no enhancement on perfusion images (E and F, two different frame). These findings are in keeping with cardiac lipoma.

Cardiac teratomas

Cardiac teratomas are rare and usually occur in children, representing the second most common primary cardiac tumor in newborns and fetal life. Cardiac teratomas derive from germ cells localized in pericardium. Usually, it is intrapericardial and attached to

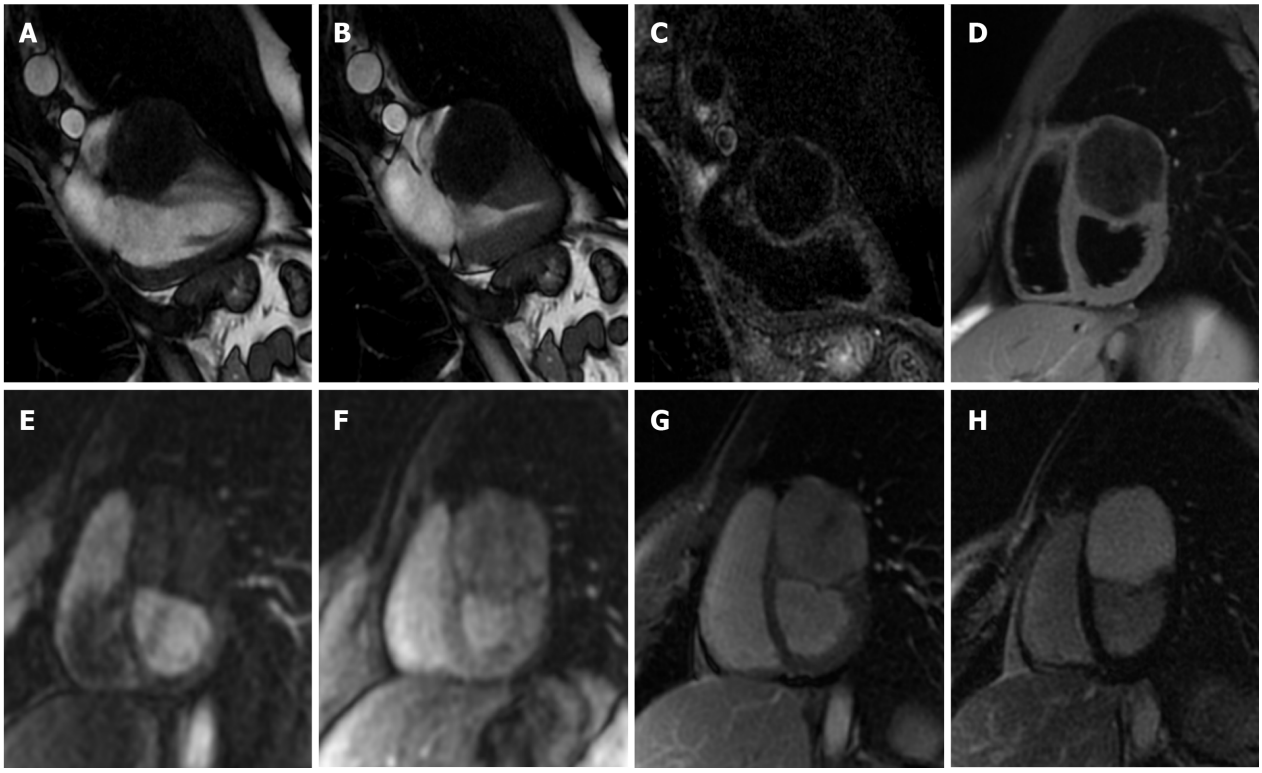

Figure 10 Twenty-five-year-old male patient with a ventricular mass of uncertain significance on computed tomography scan performed after an episode of dyspnea and chest pain. The cardiovascular magnetic resonance demonstrates a well-defined, solitary solid mass with intramural growth in the anterior wall of the left ventricle (A and B, cine steady state free precession diastolic and systolic frame, respectively). The mass shows homogeneous hypointense signal on short tau inversion recovery (C) and T1-weighted images (D). Homogeneous contrast uptake during perfusion sequences (E and F, two different frame of the perfusion sequence) and homogeneous hyperintensity in the early (G) and late gadolinium enhancement images (H). These findings are in keeping with cardiac fibroma. The patient finally underwent cardiac surgery, and the final histopathological diagnosis confirmed the radiological suspicion.

pulmonary artery and aorta and can compress SVC and RA. Intramyocardial teratoma is extremely rare and often manifests with congestive heart failure. Surgery is the treatment of choice. Recurrence or malignant degeneration is rare[68].

Typically, imaging modalities show an intrapericardial multilocular mass with cystic and solid components near aorta and pulmonary artery. On CMR, teratomas may appear iso- or hypointense on T1-weighted images, hyperintense on T2-weighted images and hypointense on first-pass myocardial perfusion imaging, with this latter allowing to differentiate them from hemangiomas. After contrast injection teratomas appear hypointense on first pass perfusion, with heterogeneous LGE[69].

Paragangliomas

Paragangliomas are extremely rare, with an incidence varying between 1.5-9 cases per million people, and it is higher in the fourth decade of life. Up to a third of them may be familial, which makes important a proper family screening. Cardiac paragangliomas represent up to 2% of all paragangliomas[70,71].

They are chromaffin-cell tumors that arise from parasympathetic or sympathetic ganglia of neural crest cells localized outside adrenal glands. They may present as a cardiac mass associated with hypertension and/or palpitation. Echocardiography, computed tomography and CMR can provide valuable anatomical and tissue characterizations, however laboratory investigations such as urine and blood tests for analysis of catecholamines and catecholamines metabolites are required to assess the diagnosis[72] .

CMR shows hypointense signal on T1 weighted images and hyperintense signal on T2 with "salt and pepper" appearance on both T1 and T2 weighted sequences; salt represents hemoglobin degradation products from intralesional hemorrhage and pepper depends on flow voids due to high vascularity. Paragangliomas show strong and early contrast enhancement after gadolinium injection, which follows the arterial vessels enhancement[72]. These tumors are characterized by peripheral LGE, due to tumor necrosis.

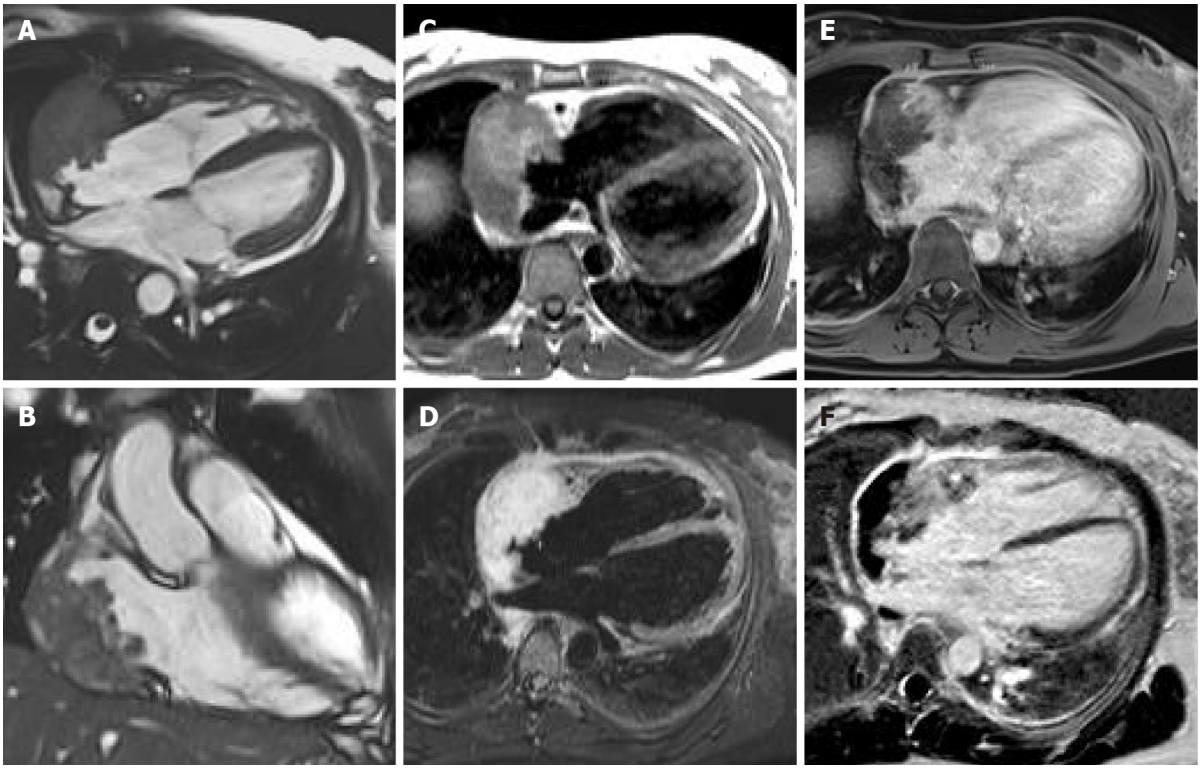

Figure 11 Sixty-five-year-old female patient with transthoracic echocardiogram finding of irregular mass originates from the right atrium wall with intracavitary expansion. Cardiovascular magnetic resonance with cine-steady state free precession images (A and B) confirms the presence of an infiltrative atrial mass in the proximity of atrio-ventricular sulcus. T1-weighted and short tau inversion recovery images (C and D, respectively) show an heterogenous hyperintense signal intensity due to complex composition of the mass. The mass shows inhomogeneous enhancement at early gadolinium enhancement and late gadolinium enhancement sequences (E and F, respectively). These findings are in keeping with a malignant primary cardiac tumor. The patient underwent myocardial biopsy with diagnosis of angiosarcoma.

Biopsy is contraindicated in these hyper-vascularized tumors due to the high risk of life-threatening bleeding.

NEOPLASTIC–MALIGNANT: PRIMARY CARDIAC TUMOR

Table 2 shows the CMR characteristics of cardiac masses that facilitates the differential diagnosis between benign and malignant masses.

Sarcomas

Angiosarcoma is the most common cardiac mass and accounts approximately for 30% of malignant primary cardiac tumors[73]. It occurs mainly in the middle-aged adults and males are more often affected than females at a ratio of 2:1. Angiosarcoma is highly aggressive neoplasm characterized by rapid local spread and distant metastases. In approximately 75% of cases, angiosarcomas are located in RA close to atrio-ventricular sulcus[19]. However, as mentioned above, the loco-regional infiltration with involvement of pericardium, tricuspid valve, SVC, right ventricle and right coronary artery is also common[19]. It can cause symptoms such as chest pain and arrhythmias. The most common site of metastasis of angiosarcoma is lung followed by liver and brain[74].

The CMR characteristic of angiosarcoma reflects the heterogenous composition of angiosarcoma characterized by high vascularization, necrosis, hemorrhage and calcification[19]. T1 and T2 weighted images show heterogenous hyperintense signal intensity due to complex composition of mass with marked enhancement after contrast medium injection due to hyper vascularized nature of the mass[19] (Figure 11).

Leiomyosarcoma usually represent the 8%-9% of cardiac sarcomas and is associated with a worst prognosis in 6-14 mo[19,75]. In 60% of cases, leiomyosarcoma involve the LA followed by the involvement of right ventricle, RA and left ventricle[19]. Similar to other cardiac masses the main problems caused by tumors are mainly due to loco-regional invasion. The presence of leiomyosarcoma in the LA can cause pulmonary

Table 2 Malignant tumor characteristic

Size	More than 5 cm
Number	More than one
Location	Right heart involvement or more than one cardiac chamber
Implantation	Broad base of implantation
Infiltration	Direct infiltration of structures such as myocardium, valves, epicardial fat and pericardial leaflets
Effusion	Pericardial or pleural hemorrhagic effusion
Signal intensity	Heterogeneous signal intensity in T1-weighted and T2-weighted images
Perfusion	Heterogeneous enhancement
EGE and LGE	Heterogeneous enhancement

EGE: Early gadolinium enhancement; LGE: Late gadolinium enhancement.

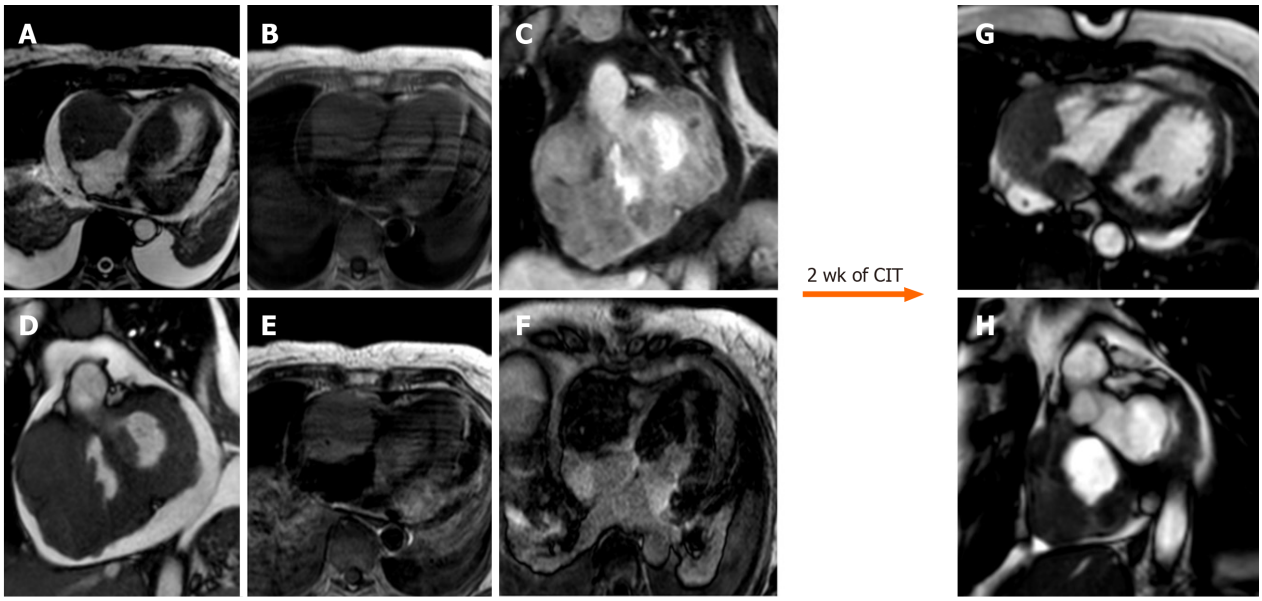

Figure 12 Sixty-five-year-old female with transthoracic echocardiogram finding of two masses in the left ventricle and right cavities following an episode of lipothymia. Cardiovascular magnetic resonance (CMR) with cine-steady state free precession images (A and B) demonstrates the presence of four distinct masses, the most voluminous mass with infiltrative features and irregular margins, extending from the right atrio-ventricular groove to both atrial and the ventricular walls. These lesions are characterized by a substantially isointense signal to cardiac muscle in T1-weighted images (C), slightly hyperintense in T2-weighted images (D) with heterogeneous enhancement at early gadolinium enhancement and relatively homogeneous hypointensity at late gadolinium enhancement images (E, F). These findings are in keeping with cardiac lymphoma. The patient underwent biopsy with a diagnosis of cardiac large B-cell lymphoma and started a chemoimmunotherapy with an excellent response as shown on CMR (G and H, cine steady state free precession) after 2 wk. CIT: Chemo-immunotherapy.

vein obstruction, pericardial effusion, chest pain, atrial arrhythmias and congestive heart failure. Furthermore, leiomyosarcoma is often characterized by rapid growth with distant metastasis and local recurrence after removal[75]. The CMR characteristics show hypo-isointense mass in T1 weighted sequences and hyperintense signal intensity in T2 weighted images[19]. LGE images show heterogenous signal intensity on post-contrast images due to hypervascular areas and necrosis[19].

Rhabdomyosarcoma represent the most common malignant cardiac mass in childhood[23]. Patients with rhabdomyosarcoma often show multiple masses, and there is not any predilection in terms of cardiac structures involved[23]. Rhabdomyosarcoma has the tendency to infiltrate the surrounding structures and in particular pericardium and valves[76]. Common symptoms include arrhythmia and heart failure sometimes associated with eosinophilia[19]. CMR shows isointense signal intensity on T1 and T2 images with hyperintense signal intensity on STIR images in presence of necrosis[23]. After the administration of contrast medium, rhabdomyosarcoma shows enhancement due to increased vascularization[19].

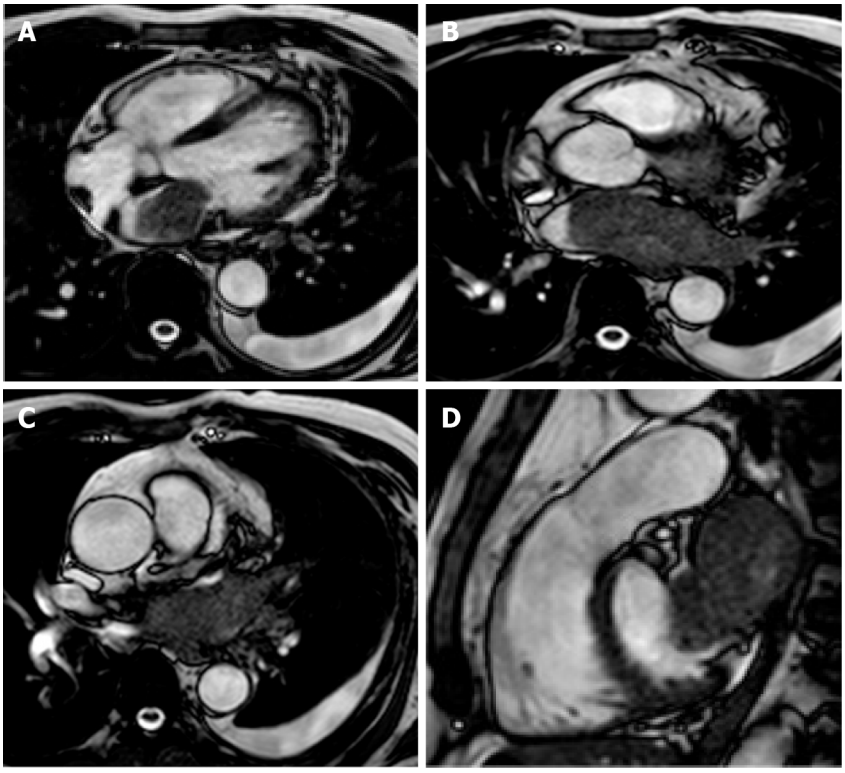

Figure 13 Sixty-five-year-old male with lung cancer. Cardiovascular magnetic resonance examination with cine-steady state free precession sequences in planes of various orientations (A-D) clearly shows infiltration of the atrium through the pulmonary veins.

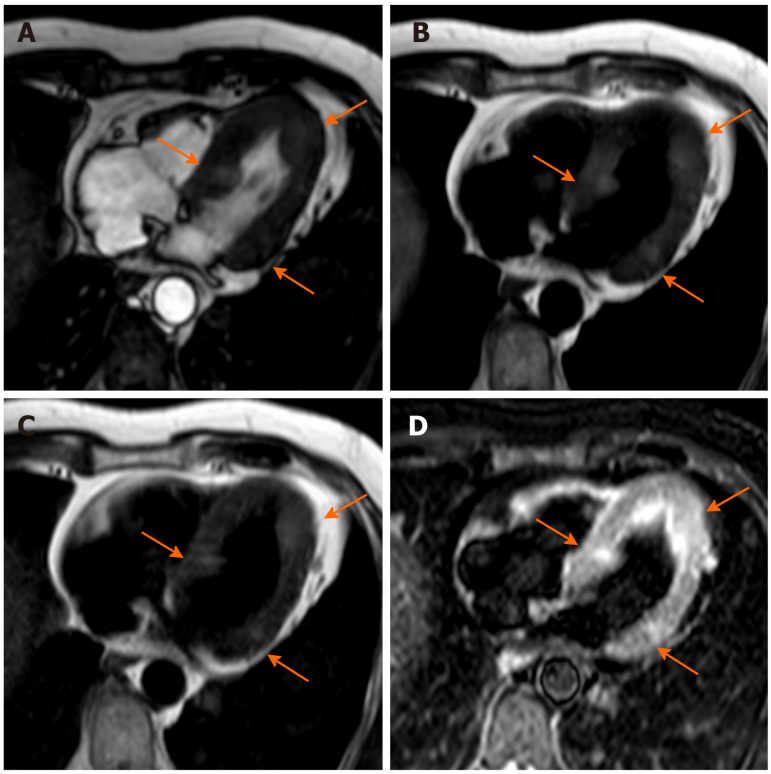

Figure 14 Sixty-four-year-old male with ocular melanoma with multiple metastases underwent cardiovascular magnetic resonance for characterization of a myocardial mass discovered at echocardiography. Nine oval nodules (three are indicated by orange arrows) with diameters ranging from 5 mm to 19 mm, slightly hyperintense in cine-steady state free precession images, T1-weighted (due to the presence of melanin) and T2-weighted sequences. The findings are in keeping with cardiac melanoma localization.

Lymphoma

Primary cardiac lymphoma usually occurs in 1.3% of primary cardiac tumors; typically arising from large B-cells in immunocompromised patients with an average age of 60-years-old[19]. Usually, masses are allocated in right chambers, often right ventricle, and are associated with pericardial effusion[63]. Despite the aggressive nature of this tumor, it shows a good response to monoclonal anti-CD20 antibody[23]. CMR images can be identified usually with the following two patterns: The first pattern shows multiple isointense masses in T1 and mildly hyperintense in T2 weighted images often located in right ventricle[77], while the second pattern is characterized by diffuse pericardial invasion of soft tissue associated with hemorrhagic effusion[23]. After administration of contrast agent, LGE usually shows no or progressive mild enhancement (Figure 12).

Mesothelioma

Pericardial mesothelioma is usually associated with asbestos exposure, and it is characterized by masses arising from pericardium, with pericardial thickening and hemorrhagic pericardial effusion[19]. Involvement of myocardium by mesothelioma is extremely rare, however protrusion of nodular mass from myocardium is suggestive for tumor invasion[19,78]. Symptoms related to pericardial mesothelioma often include breathlessness, chest pain and sometimes pericardial constriction or cardiac tamponade[23]. T1-weighted images show isointense mass, while T2-weighted images present heterogeneous hyperintense signal intensity[23]. Post-contrast images show high intense signal intensity on LGE images[23].

NEOPLASTIC–MALIGNANT: METASTATIC DISEASE

Secondary malignant cardiac tumors, also known as cardiac metastases, are cancerous tumors with spread to cardiac structures. Cardiac metastasis are very common in patients with primary tumors (usually arise from lung, breast and melanoma[12]), often clinically silent and mainly involve myocardium and pericardium[73].

Tumors can spread to the heart through four alternative pathways: Coronary arteries, lymphatic system, direct extension from nearby tissue and intracavitary diffusion through either the IVC or the pulmonary veins[23] (Figure 13).

CMR finding on tissue characterization are not specific and can change based on the metastasis component, however the most common pattern show low signal intensity on T1 and high signal intensity on T2 weighted images with high signal intensity on LGE[23]. Metastasis due to melanoma are characterized by high signal intensity on T1 weighted images[79] (Figure 14).

CONCLUSION

CMR is a fundamental radiological method in patients with suspected cardiac mass. It allows an optimal non-invasive localization of the lesion, providing multiplanar information on its relation to the surrounding structures. Moreover, with the additional feature of tissue characterization, CMR can be highly effective to distinguish pseudomasses from masses, as well as benign from malignant masses, that can also be used for differential diagnosis in the latter. Although histopathological assessment sometimes has an important role to make a definitive diagnosis, CMR is a key modality in the diagnosis of suspected cardiac masses with a great impact on patient management.

REFERENCES

1 **Aggeli C**, Dimitroglou Y, Raftopoulos L, Sarri G, Mavrogeni S, Wong J, Tsiamis E, Tsioufis C. Cardiac Masses: The Role of Cardiovascular Imaging in the Differential Diagnosis. *Diagnostics (Basel)* 2020; **10** [PMID: 33327646 DOI: 10.3390/diagnostics10121088]

2 **Kim MJ**, Jung HO. Anatomic variants mimicking pathology on echocardiography: differential diagnosis. *J Cardiovasc Ultrasound* 2013; **21**: 103-112 [PMID: 24198915 DOI: 10.4250/jcu.2013.21.3.103]

3 **Stöllberger C**, Chnupa P, Kronik G, Brainin M, Finsterer J, Schneider B, Slany J. Transesophageal echocardiography to assess embolic risk in patients with atrial fibrillation. ELAT Study Group.

Embolism in Left Atrial Thrombi. *Ann Intern Med* 1998; **128**: 630-638 [PMID: 9537936 DOI: 10.7326/0003-4819-128-8-199804150-00004]

4 **Weinsaft JW**, Kim HW, Shah DJ, Klem I, Crowley AL, Brosnan R, James OG, Patel MR, Heitner J, Parker M, Velazquez EJ, Steenbergen C, Judd RM, Kim RJ. Detection of left ventricular thrombus by delayed-enhancement cardiovascular magnetic resonance prevalence and markers in patients with systolic dysfunction. *J Am Coll Cardiol* 2008; **52**: 148-157 [PMID: 18598895 DOI: 10.1016/j.jacc.2008.03.041]

5 **L'Angiocola PD**, Donati R. Cardiac Masses in Echocardiography: A Pragmatic Review. *J Cardiovasc Echogr* 2020; **30**: 5-14 [PMID: 32766100 DOI: 10.4103/jcecho.jcecho_2_20]

6 **Rahouma M**, Arisha MJ, Elmously A, El-Sayed Ahmed MM, Spadaccio C, Mehta K, Baudo M, Kamel M, Mansor E, Ruan Y, Morsi M, Shmushkevich S, Eldessouki I, Rahouma M, Mohamed A, Gambardella I, Girardi L, Gaudino M. Cardiac tumors prevalence and mortality: A systematic review and meta-analysis. *Int J Surg* 2020; **76**: 178-189 [PMID: 32169566 DOI: 10.1016/j.ijsu.2020.02.039]

7 **Sütsch G**, Jenni R, von Segesser L, Schneider J. [Heart tumors: incidence, distribution, diagnosis. Exemplified by 20,305 echocardiographies]. *Schweiz Med Wochenschr* 1991; **121**: 621-629 [PMID: 2047823]

8 **Basso C**, Valente M, Poletti A, Casarotto D, Thiene G. Surgical pathology of primary cardiac and pericardial tumors. *Eur J Cardiothorac Surg* 1997; **12**: 730-7; discussion 737 [PMID: 9458144 DOI: 10.1016/s1010-7940(97)00246-7]

9 **Lam KY**, Dickens P, Chan AC. Tumors of the heart. A 20-year experience with a review of 12,485 consecutive autopsies. *Arch Pathol Lab Med* 1993; **117**: 1027-1031 [PMID: 8215825]

10 **Basso C**, Rizzo S, Valente M, Thiene G. Cardiac masses and tumours. *Heart* 2016; **102**: 1230-1245 [PMID: 27277840 DOI: 10.1136/heartjnl-2014-306364]

11 **Ekmektzoglou KA**, Samelis GF, Xanthos T. Heart and tumors: location, metastasis, clinical manifestations, diagnostic approaches and therapeutic considerations. *J Cardiovasc Med (Hagerstown)* 2008; **9**: 769-777 [PMID: 18607239 DOI: 10.2459/JCM.0b013e3282f88e49]

12 **Klatt EC**, Heitz DR. Cardiac metastases. *Cancer* 1990; **65**: 1456-1459 [PMID: 2306690 DOI: 10.1002/1097-0142(19900315)65:6<1456::aid-cncr2820650634>3.0.co;2-5]

13 **Bussani R**, Castrichini M, Restivo L, Fabris E, Porcari A, Ferro F, Pivetta A, Korcova R, Cappelletto C, Manca P, Nuzzi V, Bessi R, Pagura L, Massa L, Sinagra G. Cardiac Tumors: Diagnosis, Prognosis, and Treatment. *Curr Cardiol Rep* 2020; **22**: 169 [PMID: 33040219 DOI: 10.1007/s11886-020-01420-z]

14 **Poterucha TJ**, Kochav J, O'Connor DS, Rosner GF. Cardiac Tumors: Clinical Presentation, Diagnosis, and Management. *Curr Treat Options Oncol* 2019; **20**: 66 [PMID: 31250250 DOI: 10.1007/s11864-019-0662-1]

15 **Lemasle M**, Lavie Badie Y, Cariou E, Fournier P, Porterie J, Rousseau H, Petermann A, Hitzel A, Carrié D, Galinier M, Marcheix B, Lairez O. Contribution and performance of multimodal imaging in the diagnosis and management of cardiac masses. *Int J Cardiovasc Imaging* 2020; **36**: 971-981 [PMID: 32040684 DOI: 10.1007/s10554-020-01774-z]

16 **Meng Q**, Lai H, Lima J, Tong W, Qian Y, Lai S. Echocardiographic and pathologic characteristics of primary cardiac tumors: a study of 149 cases. *Int J Cardiol* 2002; **84**: 69-75 [PMID: 12104067 DOI: 10.1016/s0167-5273(02)00136-5]

17 **Buckley O**, Madan R, Kwong R, Rybicki FJ, Hunsaker A. Cardiac masses, part 1: imaging strategies and technical considerations. *AJR Am J Roentgenol* 2011; **197**: W837-W841 [PMID: 22021530 DOI: 10.2214/AJR.10.7260]

18 **Tumma R**, Dong W, Wang J, Litt H, Han Y. Evaluation of cardiac masses by CMR-strengths and pitfalls: a tertiary center experience. *Int J Cardiovasc Imaging* 2016; **32**: 913-920 [PMID: 26838354 DOI: 10.1007/s10554-016-0845-9]

19 **Li X**, Chen Y, Liu J, Xu L, Li Y, Liu D, Sun Z, Wen Z. Cardiac magnetic resonance imaging of primary cardiac tumors. *Quant Imaging Med Surg* 2020; **10**: 294-313 [PMID: 31956550 DOI: 10.21037/qims.2019.11.13]

20 **Mousavi N**, Cheezum MK, Aghayev A, Padera R, Vita T, Steigner M, Hulten E, Bittencourt MS, Dorbala S, Di Carli MF, Kwong RY, Dunne R, Blankstein R. Assessment of Cardiac Masses by Cardiac Magnetic Resonance Imaging: Histological Correlation and Clinical Outcomes. *J Am Heart Assoc* 2019; **8**: e007829 [PMID: 30616453 DOI: 10.1161/JAHA.117.007829]

21 **Pontone G**, Di Cesare E, Castelletti S, De Cobelli F, De Lazzari M, Esposito A, Focardi M, Di Renzi P, Indolfi C, Lanzillo C, Lovato L, Maestrini V, Mercuro G, Natale L, Mantini C, Polizzi A, Rabbat M, Secchi F, Secinaro A, Aquaro GD, Barison A, Francone M. Appropriate use criteria for cardiovascular magnetic resonance imaging (CMR): SIC-SIRM position paper part 1 (ischemic and congenital heart diseases, cardio-oncology, cardiac masses and heart transplant). *Radiol Med* 2021; **126**: 365-379 [PMID: 33629237 DOI: 10.1007/s11547-020-01332-6]

22 **Esposito A**, De Cobelli F, Ironi G, Marra P, Canu T, Mellone R, Del Maschio A. CMR in the assessment of cardiac masses: primary malignant tumors. *JACC Cardiovasc Imaging* 2014; **7**: 1057-1061 [PMID: 25323167 DOI: 10.1016/j.jcmg.2014.08.002]

23 **Hoey ET**, Shahid M, Ganeshan A, Baijal S, Simpson H, Watkin RW. MRI assessment of cardiac tumours: part 1, multiparametric imaging protocols and spectrum of appearances of histologically benign lesions. *Quant Imaging Med Surg* 2014; **4**: 478-488 [PMID: 25525581 DOI: 10.3978/j.issn.2223-4292.2014.11.23]

24 **Esposito A**, De Cobelli F, Ironi G, Marra P, Canu T, Mellone R, Del Maschio A. CMR in assessment

of cardiac masses: primary benign tumors. *JACC Cardiovasc Imaging* 2014; **7**: 733-736 [PMID: 25034923 DOI: 10.1016/j.jcmg.2013.11.008]

25 **Stehling MK**, Holzknecht NG, Laub G, Böhm D, von Smekal A, Reiser M. Single-shot T1- and T2-weighted magnetic resonance imaging of the heart with black blood: preliminary experience. *MAGMA* 1996; **4**: 231-240 [PMID: 9220412 DOI: 10.1007/BF01772011]

26 **Simonetti OP**, Finn JP, White RD, Laub G, Henry DA. "Black blood" T2-weighted inversion-recovery MR imaging of the heart. *Radiology* 1996; **199**: 49-57 [PMID: 8633172 DOI: 10.1148/radiology.199.1.8633172]

27 **Kübler D**, Gräfe M, Schnackenburg B, Knosalla C, Wassilew K, Hassel JH, Ivanitzkaja E, Messroghli D, Fleck E, Kelle S. T1 and T2 mapping for tissue characterization of cardiac myxoma. *Int J Cardiol* 2013; **169**: e17-e20 [PMID: 24063917 DOI: 10.1016/j.ijcard.2013.08.116]

28 **Nasser SB**, Doeblin P, Doltra A, Schnackenburg B, Wassilew K, Berger A, Gebker R, Bigvava T, Hennig F, Pieske B, Kelle S. Cardiac Myxomas Show Elevated Native T1, T2 Relaxation Time and ECV on Parametric CMR. *Front Cardiovasc Med* 2020; **7**: 602137 [PMID: 33330663 DOI: 10.3389/fcvm.2020.602137]

29 **Motwani M**, Kidambi A, Herzog BA, Uddin A, Greenwood JP, Plein S. MR imaging of cardiac tumors and masses: a review of methods and clinical applications. *Radiology* 2013; **268**: 26-43 [PMID: 23793590 DOI: 10.1148/radiol.13121239]

30 **Carson W**, Chiu SS. Image in cardiovascular medicine. Eustachian valve mimicking intracardiac mass. *Circulation* 1998; **97**: 2188 [PMID: 9626182 DOI: 10.1161/01.cir.97.21.2188]

31 **D'Amato N**, Pierfelice O, D'Agostino C. Crista terminalis bridge: a rare variant mimicking right atrial mass. *Eur J Echocardiogr* 2009; **10**: 444-445 [PMID: 19074158 DOI: 10.1093/ejechocard/jen316]

32 **McKay T**, Thomas L. 'Coumadin ridge' in the left atrium demonstrated on three dimensional transthoracic echocardiography. *Eur J Echocardiogr* 2008; **9**: 298-300 [PMID: 17127097 DOI: 10.1016/j.euje.2006.10.002]

33 **Heyer CM**, Kagel T, Lemburg SP, Bauer TT, Nicolas V. Lipomatous hypertrophy of the interatrial septum: a prospective study of incidence, imaging findings, and clinical symptoms. *Chest* 2003; **124**: 2068-2073 [PMID: 14665481 DOI: 10.1378/chest.124.6.2068]

34 **Vaitkus PT**, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 1993; **22**: 1004-1009 [PMID: 8409034 DOI: 10.1016/0735-1097(93)90409-t]

35 **Dooms GC**, Higgins CB. MR imaging of cardiac thrombi. *J Comput Assist Tomogr* 1986; **10**: 415-420 [PMID: 3700741]

36 **DeGroat TS**, Parameswaran R, Popper PM, Kotler MN. Left ventricular thrombi in association with normal left ventricular wall motion in patients with malignancy. *Am J Cardiol* 1985; **56**: 827-828 [PMID: 2998172 DOI: 10.1016/0002-9149(85)91160-9]

37 **Elen E**, D'Angelo T, Tjubandi A, Raharjo SB. A rare case of superior vena cava lipoma: its presentation from non-invasive examination. *Eur Heart J Cardiovasc Imaging* 2019; **20**: 1183 [PMID: 31329824 DOI: 10.1093/ehjci/jez085]

38 **Jungehülsing M**, Sechtem U, Theissen P, Hilger HH, Schicha H. Left ventricular thrombi: evaluation with spin-echo and gradient-echo MR imaging. *Radiology* 1992; **182**: 225-229 [PMID: 1727287 DOI: 10.1148/radiology.182.1.1727287]

39 **D'Angelo T**, Mazziotti S, Inserra MC, De Luca F, Agati S, Magliolo E, Pathan F, Blandino A, Romeo P. Cardiac Inflammatory Myofibroblastic Tumor. *Circ Cardiovasc Imaging* 2019; **12**: e009443 [PMID: 31500449 DOI: 10.1161/CIRCIMAGING.119.009443]

40 **Visser CA**, Kan G, Meltzer RS, Dunning AJ, Roelandt J. Embolic potential of left ventricular thrombus after myocardial infarction: a two-dimensional echocardiographic study of 119 patients. *J Am Coll Cardiol* 1985; **5**: 1276-1280 [PMID: 3998310 DOI: 10.1016/s0735-1097(85)80336-3]

41 **Sparrow PJ**, Kurian JB, Jones TR, Sivananthan MU. MR imaging of cardiac tumors. *Radiographics* 2005; **25**: 1255-1276 [PMID: 16160110 DOI: 10.1148/rg.255045721]

42 **Pazos-López P**, Pozo E, Siqueira ME, García-Lunar I, Cham M, Jacobi A, Macaluso F, Fuster V, Narula J, Sanz J. Value of CMR for the differential diagnosis of cardiac masses. *JACC Cardiovasc Imaging* 2014; **7**: 896-905 [PMID: 25129516 DOI: 10.1016/j.jcmg.2014.05.009]

43 **Spuentrup E**, Mahnken AH, Kühl HP, Krombach GA, Botnar RM, Wall A, Schaeffter T, Günther RW, Buecker A. Fast interactive real-time magnetic resonance imaging of cardiac masses using spiral gradient echo and radial steady-state free precession sequences. *Invest Radiol* 2003; **38**: 288-292 [PMID: 12750618 DOI: 10.1097/01.RLI.0000064784.68316.34]

44 **Paydarfar D**, Krieger D, Dib N, Blair RH, Pastore JO, Stetz JJ Jr, Symes JF. In vivo magnetic resonance imaging and surgical histopathology of intracardiac masses: distinct features of subacute thrombi. *Cardiology* 2001; **95**: 40-47 [PMID: 11385191 DOI: 10.1159/000047342]

45 **LE ROUX BT**. Pericardial coelomic cysts. *Thorax* 1959; **14**: 27-35 [PMID: 13635642 DOI: 10.1136/thx.14.1.27]

46 **Stoller JK**, Shaw C, Matthay RA. Enlarging, atypically located pericardial cyst. Recent experience and literature review. *Chest* 1986; **89**: 402-406 [PMID: 3948553 DOI: 10.1378/chest.89.3.402]

47 **Davis RD Jr**, Oldham HN Jr, Sabiston DC Jr. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. *Ann Thorac Surg* 1987; **44**: 229-237 [PMID: 2820323 DOI: 10.1016/s0003-4975(10)62059-0]

48 **Sechtem U**, Tscholakoff D, Higgins CB. MRI of the abnormal pericardium. *AJR Am J Roentgenol* 1986; **147**: 245-252 [PMID: 3487936 DOI: 10.2214/ajr.147.2.245]

49 **Verhaert D**, Gabriel RS, Johnston D, Lytle BW, Desai MY, Klein AL. The role of multimodality imaging in the management of pericardial disease. *Circ Cardiovasc Imaging* 2010; **3**: 333-343 [PMID: 20484113 DOI: 10.1161/CIRCIMAGING.109.921791]

50 **Parmar YJ**, Shah AB, Poon M, Kronzon I. Congenital Abnormalities of the Pericardium. *Cardiol Clin* 2017; **35**: 601-614 [PMID: 29025550 DOI: 10.1016/j.ccl.2017.07.012]

51 **Shah BN**, Babu-Narayan S, Li W, Rubens M, Wong T. Severe mitral annular calcification: insights from multimodality imaging. *Tex Heart Inst J* 2014; **41**: 245-247 [PMID: 24808796 DOI: 10.14503/THIJ-12-3028]

52 **Caduff JH**, Hernandez RJ, Ludomirsky A. MR visualization of aortic valve vegetations. *J Comput Assist Tomogr* 1996; **20**: 613-615 [PMID: 8708066 DOI: 10.1097/00004728-199607000-00021]

53 **Dursun M**, Yilmaz S, Ali Sayin O, Olgar S, Dursun F, Yekeler E, Tunaci A. A rare cause of delayed contrast enhancement on cardiac magnetic resonance imaging: infective endocarditis. *J Comput Assist Tomogr* 2005; **29**: 709-711 [PMID: 16163048 DOI: 10.1097/01.rct.0000177520.02175.28]

54 **Doherty NE**, Siegel RJ. Cardiovascular manifestations of systemic lupus erythematosus. *Am Heart J* 1985; **110**: 1257-1265 [PMID: 3907317 DOI: 10.1016/0002-8703(85)90023-7]

55 **Kono T**, Koide N, Hama Y, Kitahara H, Nakano H, Suzuki J, Isobe M, Amano J. Expression of vascular endothelial growth factor and angiogenesis in cardiac myxoma: a study of fifteen patients. *J Thorac Cardiovasc Surg* 2000; **119**: 101-107 [PMID: 10612767 DOI: 10.1016/s0022-5223(00)70223-6]

56 **Colin GC**, Dymarkowski S, Gerber B, Michoux N, Bogaert J. Cardiac myxoma imaging features and tissue characteristics at cardiovascular magnetic resonance. *Int J Cardiol* 2016; **202**: 950-951 [PMID: 26493410 DOI: 10.1016/j.ijcard.2015.10.111]

57 **Colin GC**, Gerber BL, Amzulescu M, Bogaert J. Cardiac myxoma: a contemporary multimodality imaging review. *Int J Cardiovasc Imaging* 2018; **34**: 1789-1808 [PMID: 29974293 DOI: 10.1007/s10554-018-1396-z]

58 **Carney JA**. Carney complex: the complex of myxomas, spotty pigmentation, endocrine overactivity, and schwannomas. *Semin Dermatol* 1995; **14**: 90-98 [PMID: 7640202 DOI: 10.1016/s1085-5629(05)80003-3]

59 **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]

60 **Syed IS**, Feng D, Harris SR, Martinez MW, Misselt AJ, Breen JF, Miller DV, Araoz PA. MR imaging of cardiac masses. *Magn Reson Imaging Clin N Am* 2008; **16**: 137-164, vii [PMID: 18474324 DOI: 10.1016/j.mric.2008.02.009]

61 **Kelle S**, Chiribiri A, Meyer R, Fleck E, Nagel E. Images in cardiovascular medicine. Papillary fibroelastoma of the tricuspid valve seen on magnetic resonance imaging. *Circulation* 2008; **117**: e190-e191 [PMID: 18347215 DOI: 10.1161/CIRCULATIONAHA.107.729731]

62 **Cannavale G**, Francone M, Galea N, Vullo F, Molisso A, Carbone I, Catalano C. Fatty Images of the Heart: Spectrum of Normal and Pathological Findings by Computed Tomography and Cardiac Magnetic Resonance Imaging. *Biomed Res Int* 2018; **2018**: 5610347 [PMID: 29503824 DOI: 10.1155/2018/5610347]

63 **Grebenc ML**, Rosado de Christenson ML, Burke AP, Green CE, Galvin JR. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. *Radiographics* 2000; **20**: 1073-103; quiz 1110 [PMID: 10903697 DOI: 10.1148/radiographics.20.4.g00jl081073]

64 **Oshima H**, Hara M, Kono T, Shibamoto Y, Mishima A, Akita S. Cardiac hemangioma of the left atrial appendage: CT and MR findings. *J Thorac Imaging* 2003; **18**: 204-206 [PMID: 12867820 DOI: 10.1097/00005382-200307000-00012]

65 **Tao TY**, Yahyavi-Firouz-Abadi N, Singh GK, Bhalla S. Pediatric cardiac tumors: clinical and imaging features. *Radiographics* 2014; **34**: 1031-1046 [PMID: 25019440 DOI: 10.1148/rg.344135163]

66 **Burke A**, Virmani R. Pediatric heart tumors. *Cardiovasc Pathol* 2008; **17**: 193-198 [PMID: 18402818 DOI: 10.1016/j.carpath.2007.08.008]

67 **Burke AP**, Rosado-de-Christenson M, Templeton PA, Virmani R. Cardiac fibroma: clinicopathologic correlates and surgical treatment. *J Thorac Cardiovasc Surg* 1994; **108**: 862-870 [PMID: 7967668]

68 **Günther T**, Schreiber C, Noebauer C, Eicken A, Lange R. Treatment strategies for pediatric patients with primary cardiac and pericardial tumors: a 30-year review. *Pediatr Cardiol* 2008; **29**: 1071-1076 [PMID: 18600370 DOI: 10.1007/s00246-008-9256-6]

69 **Ghadimi Mahani M**, Lu JC, Rigsby CK, Krishnamurthy R, Dorfman AL, Agarwal PP. MRI of pediatric cardiac masses. *AJR Am J Roentgenol* 2014; **202**: 971-981 [PMID: 24758649 DOI: 10.2214/AJR.13.10680]

70 **Ramlawi B**, David EA, Kim MP, Garcia-Morales LJ, Blackmon SH, Rice DC, Vaporciyan AA, Reardon MJ. Contemporary surgical management of cardiac paragangliomas. *Ann Thorac Surg* 2012; **93**: 1972-1976 [PMID: 22537533 DOI: 10.1016/j.athoracsur.2012.02.040]

71 **Martucci VL**, Emaminia A, del Rivero J, Lechan RM, Magoon BT, Galia A, Fojo T, Leung S, Lorusso R, Jimenez C, Shulkin BL, Audibert JL, Adams KT, Rosing DR, Vaidya A, Dluhy RG, Horvath KA, Pacak K. Succinate dehydrogenase gene mutations in cardiac paragangliomas. *Am J Cardiol* 2015; **115**: 1753-1759 [PMID: 25896150 DOI: 10.1016/j.amjcard.2015.03.020]

72 **Joynt KE**, Moslehi JJ, Baughman KL. Paragangliomas: etiology, presentation, and management. *Cardiol Rev* 2009; **17**: 159-164 [PMID: 19525677 DOI: 10.1097/CRD.0b013e3181a6de40]

73 **Butany J**, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. *Lancet Oncol* 2005; **6**: 219-228 [PMID: 15811617 DOI: 10.1016/S1470-2045(05)70093-0]

74 **Kim CH**, Dancer JY, Coffey D, Zhai QJ, Reardon M, Ayala AG, Ro JY. Clinicopathologic study of 24 patients with primary cardiac sarcomas: a 10-year single institution experience. *Hum Pathol* 2008; **39**: 933-938 [PMID: 18538171 DOI: 10.1016/j.humpath.2007.12.018]

75 **Andersen RE**, Kristensen BW, Gill S. Cardiac leiomyosarcoma, a case report. *Int J Clin Exp Pathol* 2013; **6**: 1197-1199 [PMID: 23696944]

76 **Gilkeson RC**, Chiles C. MR evaluation of cardiac and pericardial malignancy. *Magn Reson Imaging Clin N Am* 2003; **11**: 173-186, viii [PMID: 12797518 DOI: 10.1016/s1064-9689(02)00047-8]

77 **Ryu SJ**, Choi BW, Choe KO. CT and MR findings of primary cardiac lymphoma: report upon 2 cases and review. *Yonsei Med J* 2001; **42**: 451-456 [PMID: 11519090 DOI: 10.3349/ymj.2001.42.4.451]

78 **Loire R**, Tabib A. [Malignant mesothelioma of the pericardium. An anatomo-clinical study of 10 cases]. *Arch Mal Coeur Vaiss* 1994; **87**: 255-262 [PMID: 7802534]

79 **Mousseaux E**, Meunier P, Azancott S, Dubayle P, Gaux JC. Cardiac metastatic melanoma investigated by magnetic resonance imaging. *Magn Reson Imaging* 1998; **16**: 91-95 [PMID: 9436953 DOI: 10.1016/s0730-725x(97)00200-2]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com