Iron overload and arrhythmias: Influence of confounding factors

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Abstract
Arrhythmias as a cardiac complication of iron overload (IO) have been well described for decades in the clinical literature. They are assumed to be directly associated with the myocardial accumulation of iron. However, the influence of heart failure and elevated oxidative stress, which are major arrhythmogenic confounding factors associated with IO on arrhythmias, has not been critically reviewed in the published literature. A comprehensive narrative review of published articles in PubMed was conducted to address the influence of confounding factors of IO on arrhythmias. The previous data may have been largely confounded by the other cardiac complications of IO, particularly heart failure. The previous studies on IO-related arrhythmias lack proper age-gender-matched control subjects and/or comparison groups with properly controlled confounding factors to assess accurately their etiology and clinical significance. Given the above considerations, further mechanistic investigations to clarify the etiology and clinical relevance of IO-induced arrhythmias are needed. In addition, investigations to develop arrhythmia management strategy specific to IO, are warranted.

KEYWORDS
arrhythmias, heart failure, hemochromatosis, iron overload, oxidative stress

1 INTRODUCTION

Patients with iron overload (IO) have been investigated for many decades in order to demarcate the cardiac toxicity of this element.1,2 Among these studies, the potential for IO to induce or be associated with arrhythmias has been well recognized.2,4 In particular, arrhythmias associated with IO in β-thalassemia have been widely studied.2,4 However, there is a paucity of information identifying the mechanisms responsible for these arrhythmias. Namely, the previous literature has often not defined whether the mechanism is related to IO accumulation per se (ie, direct effects of the physical presence of iron on or in cardiomyocytes), a cardiomyopathic mechanism induced by heart failure secondary to IO, elevated oxidative stress secondary to increased either systemic or myocardial IO, or a combination of these. Moreover, clinical management of possible IO-induced arrhythmias is based on largely empirical observations secondary to investigators’ experiences and standard arrhythmia management guidelines from professional cardiology societies.5,6 Strikingly, clinical studies to support IO-specific arrhythmia management is largely absent including informative double-blind randomized clinical trials (RCT’s). The existing literature on IO-induced cardiac arrhythmias is confounded by the effects of cardiac systolic and diastolic dysfunction induced by IO as well as elevated oxidative stress secondary to IO. This observation makes it important to identify the specific contributing mechanisms to the effect of IO on arrhythmogenicity in both clinical and basic science investigations.
In this comprehensive narrative review, we have attempted to clarify what is scientifically certain about the mechanism and management of IO-induced arrhythmias and highlight the future research direction needed to fill the knowledge gap existing in the IO-induced arrhythmia literature.

2 METHODS

A comprehensive narrative review format was used. For this review, the literature listed in PubMed database from 1950 to 2018 was searched using keywords of iron overload and arrhythmia. When the denoted studies referred to a specific type of arrhythmia such as supraventricular or ventricular arrhythmia, conduction abnormality, life threatening or non-life threatening arrhythmia, it was commented on in the text when the study was cited. However, a majority of studies in this area provide no reference to the types of arrhythmia studied, but rather they have investigated a variety of undefined arrhythmias at the same time. In addition, heart failure used in this review paper was that of non-ischemic origin. No study was found to evaluate systemically heart failure of ischemic origin in addition to that caused by IO. Therefore, an ischemic origin of heart failure was either ruled out or there was no reference to it in this review.

3 EPIDEMIOLOGY

The specific makeup of the patient population with IO conditions varied between different regions and not well defined. Transfusion-related secondary IO is more common than primary iron metabolism-related IO. Secondary IO occurs in patients with hematologic disorders which require frequent transfusions such as thalassemia, myelodysplastic diseases, and sickle cell disease.

The incidence of arrhythmias associated with IO in β-thalassemia major has been well described. In 652 patients with β-thalassemia major, arrhythmias occurred in 14% of patients within 1 year of the finding of a decay constant of the combined effect of spin-spin interactions and main magnetic field inhomogeneity (T2*) < 6 msec which indicates a high level of cardiac IO by noninvasive assessment with cardiac magnetic resonance imaging (MRI). In contrast, the same authors have reported that 98% of these patients developed heart failure in 1 year if cardiac T2* < 10 msec. Given the fact that the incidence of clinically significant ventricular arrhythmias (couplets/multifocal/nonsustained tachycardia) noted in patients with congestive heart failure with reduced ejection fraction is 87%, the arrhythmia incidence noted in the IO report is confounded by the presence of heart failure and may not reflect the pure effect of IO on arrhythmias in this studied population. A higher incidence of arrhythmias in males as compared to the females in β-thalassemia patients is also reported; however, this study also showed a higher incidence of heart failure in males. Therefore, a confounding effect of heart failure by IO cannot be ignored in this study as well. To assess the incidence of arrhythmias is more challenging in IO in sickle cell patients due to a high incidence of arrhythmias in general (atrial and ventricular arrhythmias) without any indication as to whether IO was present or not.

3.1 Arrhythmias in IO without heart failure

The information whether arrhythmias occur in IO before the development of heart failure is very limited. In the primary IO condition of C282Y homozygote hereditary hemochromatosis (HH) in an asymptomatic stage without the development of heart failure, we have reported no significant increase in arrhythmias in newly diagnosed patients who have not undergone standard phlebotomy (ferritin: 1164 ± 886 μg/L, transferrin saturation 76 ± 19%, data are mean ± SD) as compared to age-gender–matched normal voluntary subjects in the NHLBI-sponsored Heart Study of Hemochromatosis. None of these newly diagnosed HH subjects showed an elevated iron level in the heart measured with cardiac MRI. In contrast, the chronically phlebotomized HH subjects showed a mild significant increase in supraventricular ectopy (nonsustained and low grade) as compared to the control group, although no heart failure was noted in this group. Although our study is a small-scale case-control study without evidence of excess iron deposition in the heart, the results raise the question of how significantly an overabundance of systemic iron accumulation per se contributes to arrhythmogenicity in patients with IO. Lu et al studied arrhythmias in Taiwanese patients with β-thalassemia whose left ventricular systolic function was largely preserved (only 4 out of 88 patients showed decreased left ventricular systolic function) and have reported that arrhythmias were significantly increased as myocardial IO, measured by T2* on cardiac MRI, progressed. This study suggests a probable association of arrhythmias with myocardial IO even before heart failure develops although this study lacked an age-gender–matched control group to compare with the disease population. However, this study also could not assess the effect of systemic iron accumulation per se on arrhythmias because there was a significant overlap between systemic IO and myocardial IO due to the study design.

Thus, we have to wait for well-designed case-control studies planned to evaluate the incidence of arrhythmias specifically related to IO, not confounded by the other IO-induced cardiac conditions, particularly heart failure. It will also be important to determine whether systemic IO without cardiac IO is associated with an increased incidence of arrhythmias. Of note, to design such studies is anticipated to be very challenging because of the difficulty of controlling for the effect of confounding factors such as heart failure for IO in thalassemia major, and a possible high baseline rate of arrhythmias in sickle cell disease.

4 MECHANISMS

4.1 Human studies

In HH, we found, using Holter monitoring, that chronically phlebotomy asymptomatic patients showed an increase in frequency of supraventricular ectopy (nonsustained and low grade) as compared to the age-gender–matched normal subjects despite therapeutic iron
levels (Table 1). In addition, these patients did not show increased myocardial iron level as measured with cardiac MRI. We also found that the chronically treated HH patients showed significantly elevated oxidative stress levels despite therapeutic biochemical iron levels. In view of these observations, elevated oxidative stress may contribute to the increased ectopy of this patient group. Importantly, these patients showed normal left ventricular systolic function and did not fill the criteria for grade I or above left ventricular diastolic dysfunction, negating the influence of cardiac dysfunction caused by IO. Of note, this population did show augmentation of left atrial contractile function, but its clinical significance is unknown at present.

Interestingly, although the study was based on questionnaires and physician interviews, Waalen et al could not find a significant difference in the clinical history of arrhythmias between HH patients with C282Y homozygosity and age-gender-matched control subjects. Frequent arrhythmias have been reported in IO patients with β-thalassemia; however, these studies did not provide appropriate age-gender-matched control subjects or mechanistic insights. For instance, Hamed et al showed that left atrial diameter, left ventricular interventricular septal diameter, left ventricular posterior wall thickness, and ferritin values were higher and cardiac T2* was lower (more myocardial iron content) in the patients who developed arrhythmias as compared to who did not in a pediatric population of β-thalassemia major. However, the averaged left ventricular ejection fraction was 5% lower in the former group as compared to the latter (P = 0.077) although it was in the normal range, and this finding raises concerns as to whether or not this study was confounded by the effect of IO on cardiac function. van der Bijl emphasized in their review article that arrhythmia risks increased as more iron deposition was found in the heart measured with cardiac MRI derived T2*; however, they did not examine confounding factors such as heart failure and elevated oxidative stress seen in IO. In addition, Pepe et al reported that the presence or absence of myocardial IO measured with cardiac MRI did not affect the incidence of supraventricular and ventricular hyperkinetic arrhythmias (also known as tachyarrhythmias) in the thalassemia major patients without diabetes, and myocardial IO actually decreased hyperkinetic arrhythmias in those patients with diabetes. However, they did not investigate whether myocardial IO affected the incidence of hyperkinetic arrhythmias in the entire group of thalassemia patients and whether heart failure and/or oxidative stress affected the patients with hyperkinetic arrhythmias. Thus, their studies do not answer the question whether iron overload per se is a determinant factor in developing arrhythmias in IO patients. Similarly, the same group reported that there is no significant difference in myocardial iron levels measured with T2* by cardiac MRI between transfusion-dependent thalassemia major patients with arrhythmias and those without arrhythmias. Again, this study did not assess the confounding factors of heart failure and oxidative stress.

### 4.2 Animal experiments

Animal studies of IO show conflicting results of its effect on arrhythmias. A pioneer study by Rosenmund et al (Table 2) showed a significant slowing of conduction in the heart and increased tachyarrhythmias with acute continuous venous injection of toxic doses of ferric citrate. However, this study did not provide clinically relevant information on IO-induced cardiac complications because of the toxic doses used. In this study, the effect of acute toxic IO on cardiac function and oxidative stress was not examined. Kaiser et al used IO models in guinea pigs and gerbils to evaluate the effect of IO on arrhythmias, but failed to demonstrate an increase in arrhythmias in both studies. In their latter study, over 6 months of IO was employed with a total dosage of iron 6.2 g/kg and an

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**TABLE 1** Confounding factors in clinical investigations on iron overload-induced arrhythmias

| Authors       | Ref | Year | Study type matched controls | Age-gender | Increase in arrhythmias vs control group | Presence of IO | Presence of confounding factors |
|---------------|-----|------|-----------------------------|------------|----------------------------------------|----------------|---------------------------------|
| Waalen et al  | 18  | 2002 | Case-control                | +          | –                                      | SIO NP         | NP NP                           |
| Kirk et al    | 9   | 2009 | Patient study               | –          | NA                                     | + +            | + NP                            |
| Hamed et al   | 20  | 2009 | Patient study               | –          | NA                                     | + + +/–        | NP NP                           |
| Marsella et al| 22  | 2011 | Patient study               | –          | NA                                     | + +            | + NP                            |
| Shizukuda et al| 13  | 2012 | Case-control                | + (new pts)| –                                      | + –            | +                               |
|               |     |      |                             |            | (chronic pts)                          |               |                                 |
| Lu et al      | 10  | 2013 | Patient study               | –          | NA                                     | + +            | – NP                            |
| Origa et al   | 7   | 2013 | Patient study               | –          | NA                                     | NP +            | NP NP                           |
| Pepe et al    | 21  | 2013 | Patient study               | –          | NA                                     | + +            | + NP                            |
| Pepe et al    | 8   | 2018 | Patient study               | –          | NA                                     | + +            | + NP                            |

Note: This table does not contain case reports and clinical investigations with less than 10 patient subjects.

Abbreviations: IO, iron overload; MIO, myocardial iron overload; NA, not applicable due to the absence of control group; NP, information not provided and the confounding factor presumptively not evaluated; pts, patient subjects; Ref, reference number; SIO, systemic iron overload.
estimated tissue iron around 13 mg/g dry weight. In contrast, Walker et al reported successfully inducing arrhythmias in IO gerbils with a total dosage of iron 1.9 g/kg over 8 weeks. The reported tissue iron level was around 0.55 mg/g weight (not specified dry or wet) on this study and levels were lower than that of the studies by Kaiser et al.

Although Walker et al successfully induced cardiac arrhythmias with a lesser amount of a total iron loading than that used by Kaiser et al, they did not use an arrhythmia telemetry device as Kaiser et al did and only checked ventricular ectopy during scheduled echocardiography tests without detailed description. It was in contrast to the Kaiser et al studies where an implanted telemetry device was employed and 30 minutes of recording was averaged at each measurement.

Another study was performed by Al-Rousan et al, and they reported that an increase in arrhythmias was noted in IO gerbils administered a total dosage of 1.5 g/kg iron dextran. However, ECG monitoring was obtained under anesthesia with i.p. ketamine and the IO-treated gerbils developed heart failure. The duration of ECG recording and level of oxidative stress were also unknown in this study.

Thus, the published research reports cited above are not conclusive as to whether IO per se not associated with heart failure and/or elevated oxidative stress can induce arrhythmias in experimental animals in vivo. In addition, an arrhythmogenic effect of ketamine injection could not be ruled out in some animal studies.

### 4.3 Isolated heart experiments

Laurita et al reported that conduction velocity was decreased in isolated and Langendorff apparatus perfused hearts from IO gerbils, and they observed abnormal activation patterns of paced beats due to the presence of areas of conduction block. However, this study did not evaluate cardiac function before the heart isolation preparation and thus the question remains as to whether or not this effect was solely the result of IO. Moreover, this study did not assess whether elevated oxidative stress due to IO may also play a role in the observed alterations.

Another study was performed by Al-Rousan et al, and they reported that an increase in arrhythmias was noted in IO gerbils administered a total dosage of 1.5 g/kg iron dextran. However, ECG monitoring was obtained under anesthesia with i.p. ketamine and the IO-treated gerbils developed heart failure. The duration of ECG recording and level of oxidative stress were also unknown in this study.

### 4.4 Cellular experiments

Link et al, in their pioneer study of measuring action potential in cultured IO neonatal cardiomyocytes, reported that action potential overshoot was significantly reduced without changing action potential duration in cardiomyocytes treated either with 40 µg/ml or
80 µg/ml ferric ammonium citrate in the culture media for 24 hours (Table 2). In their experiments, significant action potential irregularities, which they assumed to represent arrhythmias, developed in 2/8 experiments in the 40 µg/ml treatment group and 2/7 experiments in the 80 µg/ml treatment group. Although they did not evaluate the role of oxidative stress in this process, they speculated it to be a significant contributor to the IO-induced change in action potential overshoot.

Kuryshev et al used isolated cardiomyocytes from IO gerbils and showed a decrease in overshoot and duration of action potential, a reduction in sodium current without changing single-channel sodium current, and an increase in transient outward potassium current (Figure 1). Although the authors confirmed iron deposition in cardiomyocytes, cardiac function was not assessed in the IO gerbils before cardiomyocyte cell isolation. This consideration raises the question whether their observations on conduction abnormalities are purely based on IO or combined effects of IO and heart failure changes. They also reported that similar changes were noted in cultured neonatal rat cardiomyocytes. To obtain this result, they needed to apply at least 40 µg/mL of soluble iron for 3 days. However, this concentration of soluble iron is considered to be extremely high as compared to that of clinically managed IO patients given the fact that the majority of circulating iron exists as bound forms, particularly to transferrin in IO patients, and that non-transferrin binding iron has been more significantly associated with IO-induced cardiac complications in humans. Thus, this part of their results reflect a situation of acute iron toxicity rather than commonly noted gradual progression of IO in secondary and primary IO of humans. Moreover, the authors never conducted additional experiments to suppress the effect of oxidative stress which is elevated by this form of IO throughout the study. This omission raises a big mechanistic question whether their findings with IO are mediated by cellular iron deposition per se and/or elevated oxidative stress.

In contrast, Oudit et al reported that electrophysiologic properties of L-type Ca²⁺ channels did not change in isolated cardiomyocytes from IO mice. However, their mouse model of IO in which a 16-week period of intraperitoneal iron injection was used (a total estimated dosage of 8 g/kg) showed left ventricular systolic dysfunction; therefore, this study is also confounded by heart failure induced by IO.

Rose et al showed that the function of the Ca₃.1.3 channel which is expressed in sinoatrial node, atria, and cardiac conduction tissue, but not in ventricles was decreased in cardiomyocytes isolated from the sinoatrial node and this resulted in decreased L-type Ca²⁺ current densities and positive voltage shift in I_{Ca-L} current in this type of cardiomyocyte from the IO mouse. They suggested that this is the mechanism for reduced heart rate noted in IO conditions. However, in this study, 4 weeks of IO in the mouse from which the cell isolation was taken showed a significantly decreased left ventricular systolic function measured with echocardiography. Thus, this study did not exclude the concomitant confounding effect of heart failure on cardiomyocytes induced by IO in their findings. In addition, this study did not address whether elevated oxidative stress played a functional role in this effect of IO on sinoatrial node cardiomyocytes.
4.5 | Molecular biology experiments

The data for the delineation of molecular-based mechanisms of IO-induced arrhythmia are extremely limited in the literature. Although Kuryshnev et al found a decrease in sodium current in IO-treated gerbil cardiomyocytes, they failed to find a difference in protein expression of cardiac sodium channel proteins between IO-treated and non IO-treated cultured neonatal rat cardiomyocytes in additional experiments.32 Rose et al showed that the messenger RNA expression of the Ca\textsubscript{v}1.3 calcium channel, which was a candidate for slow heart rates in IO, was reduced. However, they could not prove this at the protein expression level.36

4.6 | Perspective

With currently available mechanistic data about IO and arrhythmias in clinical studies and various experimental studies, it is still not clear whether IO per se and/or heart failure and/or elevated oxidative stress is the etiologic factor in the genesis of the arrhythmias and conduction abnormalities. This consideration is further complicated by the fact that iron deposition occurs heterogeneously in the cardiomyocytes of IO humans1 and animals,35 as well as in cultured neonatal cardiomyocytes,37 and whether such an accumulation pattern causes an alteration of iron channels on a more universal fashion in the whole cardiomyocyte is not clear. In addition, a functional role of oxidative stress or altered contractile function of cardiomyocytes due to IO on arrhythmias has been described, but an etiologic role has still not been proven. Particularly, elevated oxidative stress which can be provoked by both iron overload per se and heart failure has been known to change functions of ion channels including both the L-type Ca channel (I\textsubscript{Ca-L}) and late sodium currents (I\textsubscript{Na-L}),38,39 and mitochondrial functions,40 which may result in arrhythmias (Figure 1). Particularly, reduction in sodium current and a converse increase in late sodium current has been well known for its arrhythmogenic role in elevated oxidative stress.39,41 Stimulation of L-type calcium channels by oxidative stress can increase intracellular calcium concentration and could be arrhythmogenic. Of note, however, this effect may counteract the reported decreased L-type calcium channel activity induced by IO and may play a part in producing the conflicting results regarding arrhythmogenicity in IO conditions. Inhibition of the K\textsubscript{ATP} channel and downregulation of I\textsubscript{Ks}, I\textsubscript{K1}, and I\textsubscript{Ks} channels induced by elevated oxidative stress are also considered to be possible additional mechanisms producing oxidative stress-induced arrhythmias. It is also known to increase Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger (NCX) activity which potentially increases afterdepolarization and therefore, arrhythmias.39 In animal studies, an etiologic role of elevated oxidative stress in ischemia reperfusion-associated arrhythmias is well described.52,43 In human studies, interestingly, the association of elevated oxidative stress with atrial fibrillation has been documented in the postsurgical period.54,45 This is an interesting finding because atrial fibrillation is reported to be also associated with IO in humans as well,46,47 in which oxidative stress is also elevated.14,15,48

Furthermore, in heart failure, cardiomyocyte pathology produces various effects that can induce arrhythmias.49-52 Among them, downregulation of the potassium current including I\textsubscript{Kr}, I\textsubscript{Ks}, and I\textsubscript{K1}, an increase in late sodium current, defective sequestration of calcium in sarcoplasmic reticulum, upregulation of calcium extrusion by electrogenic NCX which induces net inward depolarization current at the plateau phase of the action potential, and alteration of gap junction are well documented. In addition, Yano et al have reported that enhanced delayed calcium leak through ryanodine receptor2 which results in delayed afterdepolarization is another arrhythmogenic mechanism of heart failure in isolated cardiomyocytes (Figure 1).51 Recently, Morita et al have reported that the cardiac fibrosis per se seen in heart failure is a strong candidate for inducing arrhythmias.53

The link to translate findings from cellular experiments to whole animal experiments is still largely missing in IO-induced arrhythmias.34 Advancement of this field by using more advanced pharmacological and molecular approaches is needed to further understand the arrhythmogenicity of IO and its management.

5 | MANAGEMENT

The management of arrhythmias seen in IO patients is directed primarily by empirical guidelines.2,5,55 Described below are our current recommendations based on published guidelines and our clinical experience.

5.1 | Cardiac asymptomatic patients

If arrhythmias are found in cardiac asymptomatic patients, we monitor the patient and treat IO. We typically obtain echocardiography to evaluate systolic and diastolic function.3 We recommend cardiac MRI for further assessment of iron content in the heart if abnormal diastolic and/or systolic function is noted on echocardiography.3 However, other groups advocate more routine use of cardiac MRI to assess myocardial iron concentration for the management of IO, especially due to \textbeta-thalassemia.9,20 We follow standard arrhythmia management guidelines of professional cardiology societies for the management of arrhythmias in the cardiac asymptomatic individuals.56-58 We have not previously observed malignant life threatening arrhythmias in cardiac asymptomatic IO patients secondary to HH with normal left ventricular systolic function. A statistically significant increase in benign arrhythmias was only observed in chronically phlebotomy-treated HH patients as compared to age-gender-matched normal subjects.13 However, more studies are needed to assess whether our previous observation can be generalizable to the other types of IO and various duration of IO.

5.2 | Arrhythmias associated with decreased systolic cardiac function

In advanced IO patients, systolic cardiac dysfunction is a commonly encountered situation. We follow professional cardiology society
guidelines for the management of heart failure in this situation using aggressive iron removal to reverse IO. Use of a calcium channel blocker is advocated because it can block non-transferin-bound iron uptake from L-type Ca^{2+} channel in isolated cell and animal models. However, convincing clinical data to support its use in RCT's is lacking. In fact, the available evidence does not suggest that the use of calcium channel blockers is associated with a reduction in myocardial iron in patients with transfusion-dependent \(\beta\)-thalassemia. In addition, use of \(\beta\)-adrenergic blocker has been long advocated for tachyarrhythmias which are more frequent in patients with \(\beta\)-thalassemia. However, data supported by RCT's is still missing to generalize this use for arrhythmias noted in IO patients beyond its indication for cardiac systolic dysfunction. Thus, we follow currently available cardiology society clinical guidelines of heart failure to manage these arrhythmias.

### 5.3 Arrhythmias in decreased diastolic cardiac function

In this category, if the patients with arrhythmias demonstrate isolated left ventricular diastolic dysfunction, we treat the patients in accordance with current recommendations of heart failure with preserved left ventricular systolic function since there are no societal guidelines for treatment of this entity. If the patients with arrhythmias demonstrate concomitant left ventricular systolic dysfunction, we will treat them in accordance with cardiology guidelines of heart failure with reduced left ventricular systolic function.

### 5.4 Risk of arrhythmic sudden cardiac death (SCD)

The risk of arrhythmic SCD in IO patients is not well described. An increasing incidence of SCD in heart failure including that by IO is well described. Thus, the development of heart failure associated with IO should represent an alert for proper monitoring and prevention of SCD. However, recently, Russo et al reported an increase in the frequency of SCD in the patients without clinical evidence of cardiac disease in a retrospective case-control study of \(\beta\)-thalassemia patients vs controls. In this study, the IO patient population showed a significant increase in QT and JT dispersion in ECG’s, which may indicate an electrophysiological instability, as compared to the control subjects. However, this study lacked a longitudinal assessment of cardiac function and did not address whether the development of heart failure played a role in their findings. Further studies are needed to verify whether these study results are related to arrhythmias induced by IO per se or to those induced by a combination of IO, heart failure, and elevated oxidative stress in larger scale investigations. Currently, it is recommended to use a defibrillator vest for malignant ventricular arrhythmias in IO patients until IO is controlled therapeutically and assumed that the risk of SCD is diminished at that point. However, it has not been demonstrated that this approach significantly improves the clinical outcome of this population. In addition, it is unknown whether there is a difference in the frequency of SCD secondary to malignant ventricular arrhythmias noted in IO from that in various other causes of heart failure other than IO, such as hypertrophic cardiomyopathy, various infiltrative cardiomyopathies or valvular disease.

### 6 Conclusion

Our comprehensive narrative review of the literature regarding IO-related arrhythmias reveals that there is serious lack of knowledge regarding the basic mechanisms of IO-induced arrhythmias. Particularly, the link necessary to translate scientific findings noted in the cellular experiments into in vivo animal experiments of IO is missing. It also discloses that there is a large knowledge gap between our clinical consensuses and actual published scientific data for clinical management recommendations. This is a major reason that managing arrhythmias in IO patients is still largely empirical. Clinicians are largely dependent on current professional cardiology society guidelines for arrhythmias in general to treat them because those focusing on IO patients are lacking.

We hope that the research in these areas will expand and provide more precise scientific evidence in the future. More patients with IO-induced cardiac abnormalities are being identified by the advancements in genetic testing and cardiac imaging, and thus we need to design and conduct studies to fill the knowledge gap in this area.

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### Conflict of interest

The authors declare no conflict of interests for this article.

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