Received: 1 February 2019 | Revised: 24 April 2019 | Accepted: 15 May 2019

DOI: 10.1002/joa3.12208

CLINICAL REVIEW

Journal of Arrhythmia Open Access WILEY

Iron overload and arrhythmias: Influence of confounding factors

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National Institues of Health-National Heart, Lung, and Blood Institute

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.[3,4,6] Secondary IO occurs in patients with hematologic disorders which require frequent transfusions such as thalassemia, myelodysplastic diseases, and sickle cell disease.[3,4,6]

The incidence of arrhythmias associated with IO in β-thalassemia major has been well described.[7–10] 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.[9] 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%,[11] 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[8]; 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.[12]

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 (ferrtin: 1164 ± 886 μg/L, transferrin saturation 76 ± 19%, data are mean ± SD) as compared to age-gender–matched normal volunteer subjects in the NHLBI-sponsored *Heart Study of Hemochromatosis*.[13] None of these newly diagnosed HH subjects showed an elevated iron level in the heart measured with cardiac MRI.[13] 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.[13] 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.[10] 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,[9] and a possible high baseline rate of arrhythmias in sickle cell disease.[12]

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).[13] In addition, these patients did not show increased myocardial iron level as measured with cardiac MRI.[13] We also found that the chronically treated HH patients showed significantly elevated oxidative stress levels despite therapeutic biochemical iron levels.[14] In view of these observations, elevated oxidative stress may contribute to the increased ectopy of this patient group.[14,15] 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.[16,17] Of note, this population did show augmentation of left atrial contractile function, but its clinical significance is unknown at present.[17]

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.[18] 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.[19,20] 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.[20] 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.[20] 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*[19]; 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.[21] 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.[21] 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.[22] 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.[23] 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[24] and gerbils[25] 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[25] with a total dosage of iron 6.2 g/kg and an

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	
						SIO	MIO	Heart failure	Oxidative stress
Waalen et al	18	2002	Case-control	+	–	NP	NP	NP	NP
Kirk et al	9	2009	Patient study	–	NA	+	+	+	NP
Hamed et al	20	2009	Patient study	–	NA	+	+	+/–	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
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.

TABLE 2 Confounding factors in basic science investigations on iron overload-induced arrhythmias

Authors	Ref	Year	Model	Species	Effect of IO on arrhythmias	Presence of confounding factors	
						Heart failure	Oxidative stress
Rosenmund et al	23	1988	In vivo heart	rat	+	NP	NP
Link et al	31	1989	Cultured neonatal CM	rat	+	NP	NP
Kuryshev et al	32	1999	Cultured neonatal CM	rat	+	NP	NP
			Isolated CM	gerbil	+	NP	NP
Schwartz et al	30	2002	Isolated heart tissue	guinea pig	+	–	NP
Laurita et al	29	2003	Isolated heart in perfusion	gerbil	+	NP	NP
Oudit et al	35	2003	Isolated CM	mouse	–	+	+
Kaiser et al	24	2007	In vivo heart	guinea pig	–	NP	NP
Kaiser et al	25	2009	In vivo heart	gerbil	–	NP	NP
Walker et al	26	2009	In vivo heart	gerbil	+	+	NP
Rose et al	36	2011	Isolated sinoatrial node CM	mouse	+	+	NP
Al-Rousan et al	27	2012	In vivo heart	gerbil	+	+	NP

Abbreviations: CM, cardiomyocyte; IO, iron overload; NP, information not provided and the confounding factor presumptively not evaluated; Ref, reference number.

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.[26] 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.[26] 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.[24,25] The method used by Walker et al was likely unreliable to estimate the incidence of arrhythmias because they were only evaluated for a short-time during an echocardiogram by a method of visual recognition during applied chest pressure by an echocardiography probe, and possibly under the influence of anesthesia used to perform echocardiography.[26]

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.[27] However, ECG monitoring was obtained under anesthesia with i.p. ketamine[28] 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 arrhymogenic effect of ketamine injection[28] 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. (Table 2)[29] 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. Schwartz et al dissected heart muscle strips to measure conduction at the Purkinje fiber-papillary muscle junction from IO guinea pigs that were administered a total dosage of 0.25-0.42 g/kg iron over 2 weeks intraperitoneally.[30] They found that the conduction velocity was decreased at the highest iron dosage although there was no significant effect of IO on in vivo cardiac contractility at the highest iron loading of 1.5 g/kg in this model. Again, they did not assess for any changes in oxidative stress 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

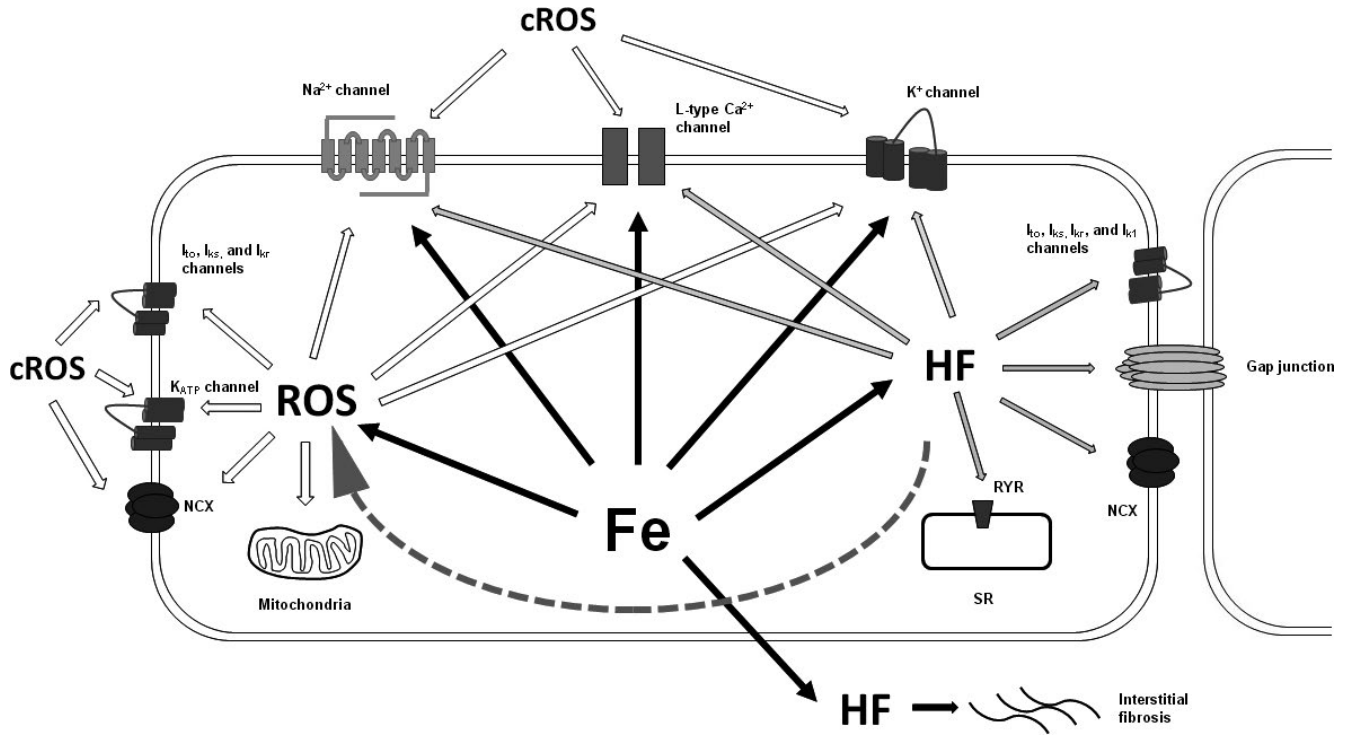

FIGURE 1 Schematic illustration of interaction of confounding factors with iron deposition (Fe) in the cardiomyocytes. ROS; oxidative stress, cROS; circulatory oxidative stress, HF; heart failure, NCX; Na^+-Ca^{2+} exchanger, RYR; rayanodine receptor, SR; sarcoplasmic reticulum

80 μg/ml ferric ammonium citrate in the culture media for 24 hours (Table 2).[31] 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.[31] 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).[32] 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.[32] 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.[33,34] 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 Ca^{2+} channels did not change in isolated cardiomyocytes from IO mice.[35] 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 $Ca_v1.3$ 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 Ca^{2+} current densities and positive voltage shift in $I_{Ca\text{-}L}$ current in this type of cardiomyocyte from the IO mouse.[36] 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.[36]

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 Kuryshev 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 $Ca_v1.3$ 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 humans[1] 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 ($I_{Ca\text{-}L}$) and late sodium currents ($I_{Na\text{-}L}$),[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_{ATP} channel and downregulation of I_{to}, I_{kr}, and I_{ks} channels induced by elevated oxidative stress are also considered to be possible additional mechanisms producing oxidative stress-induced arrhythmias.[39] It also known to increase Na^+-Ca^{2+} exchanger (NCX) activity which potentially increases afterdepolarizaton and therefore, arrhythmias.[39] In animal studies, an etiologic role of elevated oxidative stress in ischemia reperfusion-associated arrhythmias is well described.[42,43] In human studies, interestingly, the association of elevated oxidative stress with atrial fibrillation has been documented in the post-surgical period.[44,45] 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_{to}, I_{kr}, I_{ks}, and I_{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 afterdeporalization 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.[54] 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.[3,5,55] 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 patients 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 β-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[59] in this situation using aggressive iron removal to reverse IO.[3,5,55] Use of a calcium channel blocker is advocated[5] because it can block non-transferrin-bound iron uptake from L-type Ca^{2+} channel in isolated cell and animal models.[35,60] However, convincing clinical data to support its use in RCT's is lacking.[61] 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 β-thalassemia.[61] In addition, use of β-adrenergic blocker has been long advocated for tachyarrhythmias which are more frequent in patients with β-thalassemia.[5] 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.[62,63] 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.[55,59]

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.[59,64] Thus, the development of heart failure associated with IO should represent an alert for proper monitoring and prevention of SCD.[65–67] 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 β-thalassemia patients vs controls.[68] 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.[68] 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.[5] 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.

ACKNOWLEDGEMENTS

This work was supported in part by intramural programs of the National Heart, Lung, and Blood Institute of the National Institutes of Health to Y.S. and D. R. R. The views expressed here represent those of the authors' only, and are not to be construed as those of the National Heart, Lung, and Blood Institute of the National Institutes of Health or the United States Government.

CONFLICT OF INTEREST

The authors declare no conflict of interests for this article.

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REFERENCES

1. Engle MA, Erlandson M, Smith CH. Late cardiac complications of chronic, severe, refractory anemia with hemochromatosis. Circulation. 1964;30:698–705.
2. Kaye SB, Owen M. Cardiac arrhythmias in thalassaemia major: evaluation of chelation treatment using ambulatory monitoring. Br Med J. 1978;1(6109):342.
3. Gujja P, Rosing DR, Tripodi DJ, Shizukuda Y. Iron overload cardiomyopathy: better understanding of an increasing disorder. J Am Coll Cardiol. 2010;56(13):1001–12.

4. Lekawanvijit S, Chattipakorn N. Iron overload thalassemic cardiomyopathy: iron status assessment and mechanisms of mechanical and electrical disturbance due to iron toxicity. Can J Cardiol. 2009;25(4):213–8.
5. Russo V, Rago A, Papa AA, Nigro G. Electrocardiographic presentation, cardiac arrhythmias, and their management in beta-thalassemia major patients. Ann Noninvasive Electrocardiol. 2016;21(4):335–42.
6. Gulati V, Harikrishnan P, Palaniswamy C, Aronow WS, Jain D, Frishman WH. Cardiac involvement in hemochromatosis. Cardiol Rev. 2014;22(2):56–68.
7. Origa R, Danjou F, Cossa S, Matta G, Bina P, Dessi C, et al. Impact of heart magnetic resonance imaging on chelation choices, compliance with treatment and risk of heart disease in patients with thalassaemia major. Br J Haematol. 2013;163(3):400–3.
8. Pepe A, Gamberini MR, Missere M, Pistoia L, Mangione M, Cuccia L, et al. Gender differences in the development of cardiac complications: a multicentre study in a large cohort of thalassaemia major patients to optimize the timing of cardiac follow-up. Br J Haematol. 2018;180(6):879–88.
9. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation. 2009;120(20):1961–8.
10. Lu MY, Peng SS, Chang HH, Yang YL, Chen CA, Jou ST, et al. Cardiac iron measurement and iron chelation therapy in patients with beta thalassaemia major: experience from Taiwan. Transfus Med. 2013;23(2):100–7.
11. Francis GS. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence and prognosis. Am J Cardiol. 1986;57(3):3B–7B.
12. Maisel A, Friedman H, Flint L, Koshy M, Prabhu R. Continuous electrocardiographic monitoring in patients with sickle-cell anemia during pain crisis. Clin Cardiol. 1983;6(7):339–44.
13. Shizukuda Y, Tripodi DJ, Zalos G, Bolan CD, Yau YY, Leitman SF, et al. Incidence of cardiac arrhythmias in asymptomatic hereditary hemochromatosis subjects with C282Y homozygosity. Am J Cardiol. 2012;109(6):856–60.
14. Shizukuda Y, Bolan CD, Nguyen TT, Botello G, Tripodi DJ, Yau YY, et al. Oxidative stress in asymptomatic subjects with hereditary hemochromatosis. Am J Hematol. 2007;82(3):249–50.
15. Shizukuda Y, Tripodi DJ, Rosing DR. Iron overload or oxidative stress? Insight into a mechanism of early cardiac manifestations of asymptomatic hereditary hemochromatosis subjects with C282Y hjomozygosity. J Cardiovasc Transl Res. 2016;9(4):400–1.
16. Shizukuda Y, Bolan CD, Tripodi DJ, Yau YY, Smith KP, Sachdev V, et al. Left ventricular systolic function during stress echocardiography exercise in subjects with asymptomatic hereditary hemochromatosis. Am J Cardiol. 2006;98(5):694–8.
17. Shizukuda Y, Bolan CD, Tripodi DJ, Yau YY, Nguyen TT, Botello G, et al. Significance of left atrial contractile function in asymptomatic subjects with hereditary hemochromatosis. Am J Cardiol. 2006;98(7):954–9.
18. Waalen J, Felitti V, Gelbart T, Ho NJ, Beutler E. Prevalence of hemochromatosis-related symptoms among individuals with mutations in the HFE gene. Mayo Clin Proc. 2002;77(6):522–30.
19. van der Bijl P, Podlesnikar T, Bax JJ, Delgado V. Sudden cardiac death risk prediction: The role of cardiac magnetic resonance imaging. Rev Esp Cardiol (Engl Ed). 2018;961–70.
20. Hamed AA, Elguindy W, Elhenawy YI, Ibrahim RH. Early cardiac involvement and risk factors for the development of arrhythmia in patients with beta-thalassemia major. J Pediatr Hematol Oncol. 2016;38(1):5–11.
21. Pepe A, Meloni A, Rossi G, Caruso V, Cuccia L, Spasiano A, et al. Cardiac complications and diabetes in thalassaemia major: a large historical multicentre study. Br J Haematol. 2013;163(4):520–7.
22. Marsella M, Borgna-Pignatti C, Meloni A, Caldarelli V, Dell'Amico MC, Spasiano A, et al. Cardiac iron and cardiac disease in males and females with transfusion-dependent thalassemia major: a T2* magnetic resonance imaging study. Haematologica. 2011;96(4):515–20.
23. Rosenmund A, Brand B, Straub PW. Hyperlactataemia, hyperkalemia and heart block in acute iron overload: the fatal role of the hepatic iron-incorporation rate in rats on ferric citrate infusions. Eur J Clin Invest. 1988;18(1):69–74.
24. Kaiser L, Davis J, Patterson J, Boyd RF, Olivier NB, Bohart G, et al. Iron does not cause arrhythmias in the guinea pig model of transfusional iron overload. Comp Med. 2007;57(4):383–9.
25. Kaiser L, Davis JM, Patterson J, Johnson AL, Bohart G, Olivier NB, et al. Iron sufficient to cause hepatic fibrosis and ascites does not cause cardiac arrhythmias in the gerbil. Transl Res. 2009;154(4):202–13.
26. Walker EM Jr, Morrison RG, Dornon L, Laurino JP, Walker SM, Studeny M, et al. Acetaminophen combinations protect against iron-induced cardiac damage in gerbils. Ann Clin Lab Sci. 2009;39(4):378–85.
27. Al-Rousan RM, Manzoor K, Paturi S, Arvapalli RK, Laurino JP, Darnon L, et al. Long-term efficacy of deferasirox in preventing cardiovascular complications in the iron-overloaded gerbil. J Cardiovasc Pharmacol Ther. 2012;17(1):117–25.
28. Bioniche Pharma USA, LLC. Product information: ketamine hydrochloride i.v., i.m. injection, ketamine hydrochloride i.v, i.m. injection. 2008.
29. Laurita KR, Chuck ET, Yang T, Dong WQ, Kuryshev YA, Brittenham GM, et al. Optical mapping reveals conduction slowing and impulse block in iron-overload cardiomyopathy. J Lab Clin Med. 2003;142(2):83–9.
30. Schwartz KA, Li Z, Schwartz DE, Cooper TG, Braselton WE. Earliest cardiac toxicity induced by iron overload selectively inhibits electrical conduction. J Appl Physiol. 2002;93(2):746–51.
31. Link G, Athias P, Grynberg A, Pinson A, Hershko C. Effect of iron loading on transmembrane potential, contraction, and automaticity of rat ventricular muscle cells in culture. J Lab Clin Med. 1989;113(1):103–11.
32. Kuryshev YA, Brittenham GM, Fujioka H, Kannan P, Shieh CC, Cohen SA, et al. Decreased sodium and increased transient outward potassium currents in iron-loaded cardiac myocytes. Implications for the arrhythmogenesis of human siderotic heart disease. Circulation. 1999;100(6):675–83.
33. Berdoukas V, Coates TD, Cabantchik ZI. Iron and oxidative stress in cardiomyopathy in thalassemia. Free Radic Biol Med. 2015;88(Pt A):3–9.
34. Piga A, Longo F, Duca L, Roggero S, Vinciguerra T, Calabrese R, et al. High nontransferrin bound iron levels and heart disease in thalassemia major. Am J Hematol. 2009;84(1):29–33.
35. Oudit GY, Sun H, Trivieri MG, Koch SE, Dawood F, Ackerley C, et al. L-type Ca^{2+} channels provide a major pathway for iron entry into cardiomyocytes in iron-overload cardiomyopathy. Nat Med. 2003;9(9):1187–94.
36. Rose RA, Sellan M, Simpson JA, Izaddoustdar F, Cifelli C, Panama BK, et al. Iron overload decreases $Ca_V1.3$-dependent L-type Ca^{2+} currents leading to bradycardia, altered electrical conduction, and atrial fibrillation. Circ Arrhythm Electrophysiol. 2011;4(5):733–42.
37. Iancu TC, Shiloh H, Link G, Bauminger ER, Pinson A, Hershko C. Ultrastructural pathology of iron-loaded rat myocardial cells in culture. Br J Exp Pathol. 1987;68(1):53–65.
38. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. J Card Fail. 2010;16(11):888–900.
39. Sovari AA. Cellular and molecular mechanisms of arrhythmia by oxidative stress. Cardiol Res Pract. 2016;2016:9656078.
40. Sripetchwandee J, KenKnight SB, Sanit J, Chattipakorn S, Chattipakorn N. Blockade of mitochondrial calcium uniporter prevents cardiac mitochondrial dysfunction caused by iron overload. Acta Physiol (Oxf). 2014;210(2):330–41.

41. Gordan R, Wongjaikam S, Gwathmey JK, Chattipakorn N, Chattipakorn SC, Xie LH. Involvement of cytosolic and mitochondrial iron in iron overload cardiomyopathy: an update. Heart Fail Rev. 2018;23(5):801–16.
42. Jeroudi MO, Hartley CJ, Bolli R. Myocardial reperfusion injury: role of oxygen radicals and potential therapy with antioxidants. Am J Cardiol. 1994;73(6):2B–7B.
43. Dhalla NS, Elmoselhi AB, Hata T, Makino N. Status of myocardial antioxidants in ischemia-reperfusion injury. Cardiovasc Res. 2000;47(3):446–56.
44. Lubbers ER, Murphy NP, Mohler PJ. Defining the links between oxidative stress-based biomarkers and postoperative atrial fibrillation. J Am Heart Assoc. 2015;4(5). https://doi.org/10.1161/JAHA.115.002110
45. Wu JH, Marchioli R, Silletta MG, Masson S, Sellke FW, Libby P, et al. Oxidative stress biomarkers and incidence of postoperative atrial fibrillation in the omega-3 fatty acids for prevention of postoperative atrial fibrillation (OPERA) trial. J Am Heart Assoc. 2015;4(5). https://doi.org/10.1161/JAHA.115.001886
46. Patane S, Marte F. Abnormal troponin I levels in a thalassemia major patient with high ferritin concentration, permanent atrial fibrillation and without acute coronary syndrome. Int J Cardiol. 2010;138(2):e24–27.
47. Zacharski LR, McKernan L, Metzger ME, Malone MG, Samnotra V, Bhargava A, et al. Remission of paroxysmal atrial fibrillation with iron reduction in haemophilia A. Haemophilia. 2010;16(5):726–30.
48. Shizukuda Y, Bolan CD, Tripodi DJ, Sachdev V, Nguyen TT, Botello G, et al. Does oxidative stress modulate left ventricular diastolic function in asymptomatic subjects with hereditary hemochromatosis? Echocardiography. 2009;26(10):1153–8.
49. Makielski JC. Late sodium current: a mechanism for angina, heart failure, and arrhythmia. Trends Cardiovasc Med. 2016;26(2):115–22.
50. Jin H, Lyon AR, Akar FG. Arrhythmia mechanisms in the failing heart. Pacing Clin Electrophysiol. 2008;31(8):1048–56.
51. Yano M, Yamamoto T, Ikeda Y, Matsuzaki M. Mechanisms of disease: Ryanodine receptor defects in heart failure and fatal arrhythmia. Nat Clin Pract Cardiovasc Med. 2006;3(1):43–52.
52. Roden DM. A surprising new arrhythmia mechanism in heart failure. Circ Res. 2003;93(7):589–91.
53. Morita N, Mandel WJ, Kobayashi Y, Karagueuzian HS. Cardiac fibrosis as a determinant of ventricular tachyarrhythmias. J Arrhythm. 2014;30(6):389–94.
54. Siri-Angkul N, Xie LH, Chattipakorn SC, Chattipakorn N. Cellular electrophysiology of iron-overloaded cardiomyocytes. Front Physiol. 2018;9:1615.
55. Cogliandro T, Derchi G, Mancuso L, Mayer MC, Pannone B, Pepe A, et al. Guideline recommendations for heart complications in thalassemia major. J Cardiovasc Med. 2008;9(5):515–25.
56. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1–76.
57. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018;72(14):1677–749.
58. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67(13):e27–e115.
59. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009;53(15):e1–e90.
60. Tsushima RG, Wickenden AD, Bouchard RA, Oudit GY, Liu PP, Backx PH. Modulation of iron uptake in heart by L-type Ca^{2+} channel modifiers: possible implications in iron overload. Circ Res. 1999;84(11):1302–9.
61. Sadaf A, Hasan B, Das JK, Colan S, Alvi N. Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia. Cochrane Database Syst Rev. 2018;7:CD011626.
62. Kazik A, Wilczek K, Polonski L. Management of diastolic heart failure. Cardiol J. 2017;17(6):558–65.
63. Tschope C, Westermann D. Heart failure with normal ejection fraction. Pathophysiology, diagnosis, and treatment. Herz. 2009;34(2):89–96.
64. Kremastinos DT, Tsetsos GA, Tsiapras DP, Karavolias GK, Ladis VA, Kattamis CA. Heart failure in beta thalassemia: a 5-year follow-up study. Am J Med. 2001;111(5):349–54.
65. Hasan A, Yancy CW. Treatment of ventricular dysrhythmias and sudden cardiac death: a guideline-based approach for patients with chronic left ventricular dysfunction. Congest Heart Fail. 2007;13(4):228–35.
66. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA III, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2012;144(6):e127–e145.
67. Epstein AE, Dimarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. Heart Rhythm. 2008;5(6):e1–62.
68. Russo V, Rago A, Pannone B, Papa AA, Di Meo F, Mayer MC, et al. Dispersion of repolarization and beta-thalassemia major: the prognostic role of QT and JT dispersion for identifying the high-risk patients for sudden death. Eur J Haematol. 2011;86(4):324–31.

How to cite this article: Shizukuda Y, Rosing DR. Iron overload and arrhythmias: Influence of confounding factors. *J Arrhythmia*. 2019;35:575–583. https://doi.org/10.1002/joa3.12208