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Substrates and potential therapeutics of ventricular arrhythmias in heart failure

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Abstract

Heart failure (HF) is a clinical syndrome characterized by ventricular contractile dysfunction. About 50% of death in patients with HF are due to fetal ventricular arrhythmias including ventricular tachycardia and ventricular fibrillation. Understanding ventricular arrhythmic substrates and discovering effective antiarrhythmic interventions are extremely important for improving the prognosis of patients with HF and reducing its mortality. In this review, we discussed ventricular arrhythmic substrates and current clinical therapeutics for ventricular arrhythmias in HF. Base on the fact that classic antiarrhythmic drugs have the limited efficacy, side effects, and proarrhythmic potentials, we also updated some therapeutic strategies for the development of potential new antiarrhythmic interventions for patients with HF.

Keywords

Antiarrhythmic drugs; Catheter ablation; Heart failure; Ventricular arrhythmia; Ventricular arrhythmic substrate

1. Introduction

Heart failure (HF) affects over 6.5 million Americans and costs the nation an estimated $31 billion each year (Benjamin et al., 2017; Heidenreich et al., 2013). There are at least 15 million patients with HF in Europe with significantly increased prevalence after 75 years of age (Mosterd and Hoes, 2007). In general, coronary heart disease is the most common cause of HF. HF is also induced by some other conditions including hypertension, faulty heart valves, myocarditis, cardiomyopathy, diabetes, hyperthyroidism, etc. Although there have been advances in understanding for HF and related pharmacological and device therapeutics, the mortality rate remains extremely high in patients with HF, with up to 50% of the patients dying suddenly (Fang et al., 2015; Go et al., 2014). Malignant ventricular arrhythmia,

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including ventricular tachycardia (VT) and ventricular fibrillation (VF) is a common complication and accounts for nearly 50–60% of mortality in patients with HF (Carson et al., 2005; Cygankiewicz et al., 2008; Doval et al., 1996; Engelstein and Zipes, 1998; Huikuri et al., 2001; Maskin et al., 1984; MERIT-HF study group, 1999; Podrid et al., 1992; Sami, 1991; Singh, 2002; Singh et al., 1997; Teerlink et al., 2000; Thompson, 2009). The management of ventricular arrhythmias is one of the clinical challenges in patients with HF. In this review, we mainly updated ventricular arrhythmic substrates and related therapeutics in the HF state.

2. Substrates for ventricular arrhythmias in HF

It is generally accepted that alterations in cardiac mechanical, morphological, metabolic, and electrophysiological properties, and neurohumoral remodeling in HF not only increase the severity of ventricular hemodynamic dysfunction, but also induce the genesis of ventricular arrhythmias. These structural and functional alterations as well as neurohumoral remodeling are considered as ventricular arrhythmic substrates (Table 1). These ventricular arrhythmic substrates cause ventricular arrhythmias through 3 cellular mechanisms including abnormal automaticity, triggered activity, and reentry. First, automaticity normally originates from the sinus node, atrioventricular node, and His-Purkinje system with the rate of phase 4 depolarization of the cardiac action potential. Abnormal automaticity in cardiomyocytes and subendocardial Purkinje fibers has been demonstrated to cause ventricular arrhythmias (Friedman et al., 1973; Lo and Hsia, 2008). Second, the most common triggered activities causing ventricular arrhythmias are early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) (Antzelevitch and Burashnikov, 2011; Weiss et al., 2010). EADs and DADs usually occur in phase 2 to 3 and phase 3 to 4 of the action potential, respectively when the action potential has a prolonged repolarization (Antzelevitch and Burashnikov, 2011; Lo and Hsia, 2008; Weiss et al., 2010). Third, when the normal electrical signal circuit is anatomically or functionally blocked, the electrical signal continually proceeds an alternative circuit looping back to form the reentry for the occurrence of ventricular arrhythmias (Antzelevitch, 2001; Lo and Hsia, 2008).

2.1. Ventricular structural and mechanical changes

In patients with coronary artery disease and animal models of myocardial infarction, the pathological process to HF leads to extensive cardiac myocyte death and results in ventricular scar regions consisting of dense fibrosis with collagen and fibrocytes (Cabin and Roberts, 1980; de Bakker et al., 1993; Lo and Hsia, 2008; Soejima et al., 2002; Stevenson, 2009). Light microscopy findings in humans demonstrated that the distribution of connexin 43 gap junctions in the border zone of the infarcted human heart are organized into transverse (side-to-side) connections but not a normal longitudinal connections (Peters et al., 1997; Peters and Wit, 1998; Peters and Wit, 2000). The ventricular scar regions and aberrant distribution of gap junctions in the border zone of infarction areas cause conduction block and propagation barrier (de Bakker et al., 1993; Peters et al., 1997; Stevenson, 2009). Microscopic data demonstrated that fibrosis in ventricular scar regions separates cardiac myocyte bundles, forcing the excitation to form a looping circuit surrounding the bundles (de Bakker et al., 1993; Stevenson, 2009). Slow conduction and fibrous anatomic barriers in

areas of infarcted myocardium create the basis of reentry for the ventricular arrhythmogenesis (Ajijola et al., 2014; de Bakker et al, 1993; Lo and Hsia, 2008; Masarone et al., 2017; Stevenson, 2009).

To improve cardiac hemodynamic functions including cardiac output, numerous compensatory reactions occur in HF. These reactions include left ventricular hypertrophy, high left ventricular filling pressure, as well as increases in cardiac preload and afterload (Masarone et al., 2017; Pye and Cobbe, 1996; Zabel et al., 1996). These mechanical changes in HF are involved in the ventricular arrhythmogenesis through influencing pro-arrhythmic electrophysiology (such as shortening of repolarization phase of action potential, cell-to-cell uncoupling, and sub-endocardial ischemia) (Masarone et al., 2017; Pye and Cobbe, 1996; Zabel et al., 1996). More importantly, the time-dependent progression of HF itself could trigger the occurrence of ventricular arrhythmias as the arrhythmic substrate (Banasik et al., 2016; Santangeli et al., 2017). Conversely, the occurrence of ventricular arrhythmias also serves as a basis of progressive pump failure in HF to maintain the vicious cycle (Neubauer, 2007; Santangeli et al., 2017).

2.2. Ventricular metabolic abnormalities

The progression of HF is accompanied with significant intracellular and extracellular ionic and metabolic changes in the myocardium (Gettes, 1992; Ghuran and Camm, 2001). There are acidosis and increases of lysophosphoglycerides, adenosine, lactate, and carbon dioxide in the extracellular fluid, whereas calcium, magnesium, and sodium ions, and cyclic adenosine monophosphate (cAMP) are increased in the intracellular fluid (Ghuran and Camm, 2001). These metabolic changes affect inward and outward transmembrane ionic current fluxes, and further result in depolarization of the resting membrane potential, slow conduction, dispersion of repolarization, and abnormal automaticity, triggering ventricular arrhythmias (Ghuran and Camm, 2001).

In the large cohort of patients with HF, Hoss, et al. demonstrated that there are 21% of the patients with high serum potassium levels and 11% of the patients with low serum potassium levels (Hoss et al., 2016). An increase in extracellular potassium decreases amplitude of the action potential and voltage of the plateau, accelerates the phase of rapid repolarization, and suppresses automaticity (Gettes, 1992). These changes of pro-arrhythmic electrophysiology cause sinus node suppression and atrioventricular block as well as ventricular reentrant arrhythmias (Gettes, 1992). A decrease in extracellular potassium increases Purkinje cell activity, shortens plateau duration in ventricular myocytes, prolongs the phase of rapid repolarization, and enhances QT dispersion and electrical heterogeneity (Gettes, 1992; Hoss et al., 2016). The electrophysiological effects of low extracellular potassium increase electrical instability, and incidence of ventricular arrhythmias and sudden cardiac death in patients with HF (Gettes, 1992; Hoss et al., 2016; Nolan et al., 1998; Thompson, 2009).

2.3. Ventricular electrophysiological changes

Studies in isolated primary ventricular myocytes from animal models and patients with HF have shown a marked prolongation of the action potential duration (APD) (Beuckelmann et al., 1993; Kaab et al., 1996; Vermeulen et al., 1994). In a mouse model with pressure

overload-induced HF, Wang, et al. demonstrated that the APD is more prolonged in ventricular subepicardial myocytes than that in ventricular subendocardial myocytes (Wang et al., 2006). In rapid ventricular pacing-induced canine HF, prolongation of the APD is markedly greater in ventricular mid-myocardial myocytes than that in ventricular subepicardial myocytes (Akar and Rosenbaum, 2003). These findings indicate presence of the transmural APD gradient and heterogeneity in prolongation of the APD in different layers of ventricular myocytes. Additionally, prolongation of the APD in isolated ventricular myocytes matches prolongation of the QT interval measured by the surface ECG, indicating the link between prolongation of the APD and changes of the QT interval (Akar and Rosenbaum, 2003). Although prolongation of the APD and its heterogeneity might trigger ventricular arrhythmias through EADs, DADs, or reentry in HF (Ebinger et al., 2005; Janse et al., 2001; Wang and Hill, 2010), thus far there is no direct evidence for the relationship among prolongation of the APD, QT prolongation, and ventricular arrhythmogenesis in HF.

Prolongation of the APD in HF is due to down-regulation of outward potassium currents, alteration of calcium channel kinetics, and increases in late sodium currents and sodium-calcium exchanger (Houser et al., 2000; Kaab et al., 1996; Kaab et al., 1998; O'Rourke et al., 1999; Pogwizd et al., 2001; Undrovinas et al., 1999; Wang et al., 2008). First, potassium channels play a pivotal role in stabilizing the resting membrane potential and repolarization phase of the action potential. Many studies have demonstrated that outward potassium currents, including transient outward potassium currents, inward rectifying potassium currents, and delayed rectifier potassium currents, are reduced in isolated ventricular myocytes from animal models and patients with HF, causing resultant slow repolarization and prolongation of the APD (Beuckelmann et al., 1993; Kaab et al., 1996; Kaab et al., 1998; Pogwizd et al., 2001; Tsuji et al., 2000). Second, voltage-gated L-type calcium channels are the primary source of calcium influx in cardiac myocytes, and secondarily induce calcium release from sarcoplasmic reticulum. Although alteration of L-type calcium currents is depending on the severity of diseases, L-type calcium currents is decreased in HF ventricular myocytes (Kamp and Hell, 2000; Pitt et al., 2006; Prestle et al., 2003; Yeh et al., 2008). Simultaneously, voltage- and calcium-dependent inactivation of L-type calcium channels is significantly slowed down in HF ventricular myocytes (Kleiman and Houser, 1988; Ryder et al., 1993; Wang et al., 2008). These changes in L-type calcium channels delay intracellular calcium transients, elevate diastolic calcium, reduce systolic calcium (Beuckelmann et al., 1992; Gwathmey et al., 1987), which contribute to prolongation of the APD in HF (Pogwizd et al., 2001; Prestle et al., 2003; Wang and Hill, 2010; Yeh et al., 2008). Third, although all isoforms of voltage-gated sodium channels are expressed in cardiac myocytes, $Na_V1.5$ channels are the most prominent and important cardiac sodium channels to generate a large inward currents and mediate rapid membrane depolarization of cardiac myocytes (Wang and Hill, 2010; Zimmer et al., 2014). In animal models and patients with HF, peak and late sodium currents are increased in ventricular myocytes (Huang et al., 2001; Jacques et al., 1997; Maltsev et al., 2007; Undrovinas et al., 1999). More importantly, the decay of late sodium currents is slowed down in failing human and canine ventricular myocytes (Maltsev et al., 2007). The changes in sodium currents are possibly involved in prolongation of the APD and resultant ventricular arrhythmogenesis in HF (Wang and Hill, 2010). Fourth, the sodium and calcium exchanger is a cell membrane protein that transports

3 sodium ions into the cell and one calcium ion out of the cell (Ginsburg et al., 2013). Some studies in animal models of HF and failing humans have shown that the mRNA and protein expressions and function of the sodium and calcium exchanger are significantly increased in ventricular myocytes (Flesch et al., 1996; Pogwizd et al., 1999; Pogwizd et al., 2001; Reinecke et al., 1996; Studer et al., 1994; Weber et al., 2003). The overactivation of sodium and calcium exchangers generates inward currents with calcium extrusion, contributing to prolongation of APD and reduced contractile function (Kho et al., 2012; Verkerk et al., 2001; Wang and Hill, 2010). Indeed, up-regulation of the sodium and calcium exchanger is accompanied by an obvious propensity easily to trigger ventricular arrhythmias through DADs in HF (Pogwizd et al., 2001; Verkerk et al., 2001; Wang and Hill, 2010).

2.4. Neurohumoral abnormalities

Excessive sympathetic activation is a major feature in patients with HF (Creager et al., 1986; Floras, 2009; Saul et al., 1988; Schwartz and De Ferrari, 2011; Triposkiadis et al., 2009), which is manifested by elevated plasma levels of epinephrine and norepinephrine and overactivation of cardiac sympathetic nerve fibers innervated the myocardium (Cohn et al., 1984; Daly and Sole, 1990; Feng et al., 1994; Tu et al., 2014; Valdemarsson et al., 1994; Zhang et al., 2017b). Some studies demonstrated cardiac sympathetic nerve hyperinnervation and increased cardiac neuronal norepinephrine release in patients with HF (Cao et al., 2000; Cao et al., 2000; Meredith et al., 1991; Meredith et al., 1993). Although there is no available information about the effect of cardiac sympathetic overactivation on cardiac electrophysiology in isolated failing myocytes due to the limitation of techniques, cardiac sympathetic overactivation contributes to HF progression, and triggers ventricular arrhythmias and sudden cardiac death as a major arrhythmic substrate (Creager et al., 1986; Du et al., 1999; Floras, 2009; Gilmour, 2001; Kalla et al., 2016; Meredith et al. 1991; Meredith et al., 1993; Podrid et al., 1990; Saul et al., 1988; Schwartz and De Ferrari, 2011; Schwartz, 2014a; Thompson, 2009; Tomaselli and Zipes, 2004; Triposkiadis et al., 2009; Zhou et al., 2008; Zipes, 2008). The role of cardiac sympathetic hyperactivation is highlighted by use of β-adrenergic receptor blockers as the key approach to the current therapy (Colucci et al., 1996; Fiuzat et al., 2012; Gheorghiade et al., 2003; Nevzorov et al., 2012; Packer et al., 1996).

Although elevated plasma levels of epinephrine and norepinephrine reflect overactivation of the peripheral sympathetic nervous system and play an important role in the pathophysiology of HF, one recent study found that circulating norepinephrine does not affect whole heart dispersion of repolarization and T-peak to T-end interval (Yagishita et al., 2015), two independent markers for ventricular arrhythmias and sudden cardiac death (Di Diego et al., 2003; Izumi et al., 2012; Opthof et al., 2007; Tanabe et al., 2001; Yagishita et al, 2015; Zhang et al., 2017a; Zhang et al., 2017b). Therefore, increased cardiac sympathetic nerve activity and resultant release of neuronal transmitters from sympathetic nerve terminals could be one key factor to trigger ventricular arrhythmogenesis in HF. Additionally, cardiac sympathetic neurons contain co-transmitters including norepinephrine and neuropeptide Y, and both norepinephrine and neuropeptide Y are highly dependent on cardiac sympathetic nerve activity (Burnstock, 2009; Warner and Levy, 1990). Neuropeptide Y is also involved in ventricular arrhythmogenesis and sudden cardiac death (Herring et al.,

2016; Kalla et al., 2014; Saleh, 2003; Zipes and Rubart, 2006). In particular, some studies have demonstrated that β-adrenergic receptor blockers do not provide satisfactory protection against sudden cardiac death, and even that some patients are either intolerant or refractory to this therapy (Bos et al., 2013; Coleman et al., 2012; Kuck et al., 2000; Moss et al., 2000; Napolitano and Priori, 2007; Priori et al., 2002; Sumitomo et al., 2003). The possible explanation for the incomplete protection of β-adrenergic receptor blockers is that β-adrenergic receptor blockers only antagonize β-adrenergic receptors but do not normalize HF-enhanced cardiac sympathetic nerve activity and resultant release of both norepinephrine and neuropeptide Y (Anderson, 2003).

Calcium channels is a key trigger for the release of both norepinephrine and neuropeptide Y from neuronal terminals (Augustine, 2001; Borst and Sakmann, 1996; Burnstock, 2009; Weber et al., 2010; Zucker, 1993). Using coronary artery ligation-induced rat HF model, Tu, et al. have demonstrated that N-type calcium currents and cell excitability in cardiac sympathetic neurons as well as cardiac sympathetic nerve activity are increased in HF rats, compared to sham rats (Tu et al., 2014). More importantly, *in vivo* lentiviral transfection of N-type calcium channel shRNA into cardiac sympathetic neurons of HF rats reduces N-type calcium currents and cell excitability in cardiac sympathetic neurons, and cardiac sympathetic nerve activity towards the level seen in sham rats (Zhang et al., 2017b). This shRNA also improves ECG markers of ventricular arrhythmogenesis (including the QT interval, QT dispersion, and T-peak to T-end interval), and decreases the incidence and duration of ventricular tachycardia/fibrillation in conscious HF rats (Zhang et al., 2017b). Therefore, it is assumed that increased N-type calcium currents in cardiac sympathetic neurons could contribute to the cardiac sympathetic neve hyperactivity and ventricular arrhythmogenesis in HF.

3. Substrate-based potential therapeutics for ventricular arrhythmias in HF

3.1. Pharmacological therapies

According to clinical observations and predominant electrophysiological effects of the drugs, antiarrhythmic drugs are classified into class I (sodium channel blockers), class II (β-adrenergic receptor blockers), class III (potassium channel blockers), and class IV (L-type calcium channel blockers) (Singh and Vaughan Williams, 1970; Vaughan Williams, 1970). However, it would be inappropriate for all types of antiarrhythmic drugs to be applied for ventricular arrhythmias in HF due to the specific circumstance in patients with HF and side effects of these antiarrhythmic drugs. The choice of antiarrhythmic drug therapy in patients with HF should be made on an individual basis and consideration of side effects.

3.1.1. Sodium and calcium channel blockers—Sodium channel blockers (mexiletine, tocainide, procainamide, quinidine, disopyramide, flecainide, and propafenone) and calcium channel blockers (verapamil, diltiazem, amlodipine, and nifedipine) should not be used in patients with HF due to their negative inotropic effects and proarrhythmic potential (Ellison et al., 2003; Flaker et al., 1992; Furberg and Yusuf, 1988; Mahe et al., 2003; Maxwell and Jenkins, 2011). These side effects could worsen HF and increase

mortality in patients with HF during clinical therapies with sodium and calcium channel blockers (Flaker et al., 1992; Furberg and Yusuf, 1988; Mahe et al., 2003; Maxwell and Jenkins, 2011; Stevenson et al., 1996).

Recent research interest is attracted by inhibition of late-sodium-currents and late-calcium-currents because HF-elevated late-sodium-currents and late-calcium-currents play an important role in the genesis of EADs and are associate with increased risk of ventricular arrhythmias (Belardinelli et al., 2015; Cooper et al., 2010; Xie et al., 2009). Animal experimental studies demonstrated that ranolazine, a compound for treatment of chronic angina, selectively inhibits late-sodium-currents but not peak-sodium currents, reduces repolarization dispersion, and suppresses EAD-triggered ventricular arrhythmias (Antzelevitch et al., 2011; Morita et al., 2011; Sicouri et al., 2008). Another highly selective late-sodium-current blocker, GS-458967 is also reported to exert antiarrhythmic effects through suppressing EAD- and DAD-induced triggered activity (Sicouri et al., 2013). Roscovitine, a purine analog can selectively inhibit late-calcium-currents but not peak-calcium currents, and prevent EAD-mediated ventricular arrhythmias (Angelini et al., 2016; Yarotskyy and Elmslie, 2007; Yazawa and Dolmetsch, 2013). More importantly, clinical studies have demonstrated that Ca/calmodulin-dependent protein kinase II (CaMKII) activation with its downstream enhances both late-sodium-currents and late-calcium-currents, and subsequently evokes EAD-mediated ventricular arrhythmias in HF (Karagueuzian et al., 2017; Swaminathan et al., 2012). These findings lead to the development of specific blockers of late-sodium-currents and late-calcium-currents for the treatment of ventricular arrhythmias in HF.

3.1.2. Potassium channel blockers—As discussed above, prolongation of the APD is a major feature in ventricular myocytes from patients with HF and failing animal models, which is associated with serious ventricular arrhythmias and sudden cardiac death in HF (Beuckelmann et al., 1993; Kaab et al., 1996; Tomaselli and Zipes, 2004; Vermeulen et al., 1994). As class III antiarrhythmic compounds, potassium channel blockers induce prolongation of the APD and likely increase mortality in patient with HF during clinical trials (Kober et al., 2000; Kober et al., 2008; MacNeil et al., 1993; Pratt et al., 1998; Santangeli et al., 2016; Santangeli et al., 2017; Waldo et al., 1996). Except amiodarone, therefore, potassium channel blockers (such as sotalol, dofetilide, dronedarone, azimilide, and celivarone) should not be considered as the effective drugs for ventricular arrhythmias in HF. Amiodarone is a major antiarrhythmic drug in HF (Massie et al., 1996; Nul et al., 1997; Singh et al., 1995) when patients with HF are intolerant of β-adrenergic blockers. Clinical trials in patients with HF demonstrated that amiodarone significantly suppresses ventricular arrhythmias, and reduces mortality and sudden cardiac death without any adverse effects (Amiodarone trials Meta-analysis investigators, 1997; Ceremuzynski et al., 1992; Lo and Hsia, 2008; Navarro-Lopez et al., 1993; Santangeli et al., 2017). The therapeutic effect of amiodarone on ventricular arrhythmias in HF might be dependent on its multiple pharmacological actions, including the blockage of cardiac sodium, potassium, and calcium channels as well as sympatholytic effects (Ellison et al., 2003). However, non-cardiac toxicity is a big concern during long-term amiodarone therapy (Amiodarone trials Meta-analysis investigators, 1997).

3.2. Autonomic therapies

As mentioned above, ventricular arrhythmogenesis is modulated by cardiac sympathetic overactivation in HF. Therapies for inhibiting cardiac sympathetic outflow and subsequently suppressing ventricular arrhythmias in HF are in clinical uses, clinical trials, or animal experimental studies. First, besides improving cardiac metabolism to benefit the management of patients with HF, β-adrenergic blockers are also first-choice antiarrhythmic drugs for ventricular arrhythmias so long as this type of the drugs is tolerated by patients with HF. Clinical trials have demonstrated that β-adrenergic blockers (such as acetabutolol, atenolol, carvedilol, metoprolol, propranolol, and timolol) markedly suppress ventricular arrhythmias and reduce mortality in patients with HF (Aronson and Burger, 2002; Cice et al., 2000; Dargie, 2001; Exner et al., 1999; Hjalmarson et al., 2000; Mcmurray, 2000; MERIT-HF study group, 1999). Second, as cotransmitter released from cardiac sympathetic nerve terminals, neuropeptide Y is associated with ventricular arrhythmogenesis and sudden cardiac death (Herring et al., 2016; Kalla et al., 2014; Saleh, 2003; Zipes and Rubart, 2006). Animal experimental studies have shown that neuropeptide Y1 receptor antagonist (BIBO3304) but not Y2 receptor antagonist (AR-H05359) reduces ventricular arrhythmias (Herring, 2015; Kalla et al., 2014; Omerovic et al., 2007), which should be a useful therapeutic strategy for ventricular arrhythmias in HF because neuropeptide Y levels are elevated in patients with HF (Hulting et al., 1990). Third, N-type calcium currents account for about 60–70% of the whole calcium currents in cardiac sympathetic neurons (Tu et al., 2014), and the release of neural transmitters (norepinephrine and neuropeptide Y) from cardiac sympathetic nerve terminals is triggered by calcium influx via N-type but not L- and P/Q-type calcium channels (Molderings et al., 2000). Recent studies have demonstrated that overactivation of N-type calcium channels in cardiac sympathetic neurons is involved in ventricular arrhythmogenesis in HF animals (Tu et al., 2014; Zhang et al., 2017b). A dual N- and L-type calcium channel blocker, cilnidipine markedly prevents fatal ventricular arrhythmias in mice with HF (Yamada et al., 2014). N-type calcium channels are only expressed in neurons, but not in non-neuronal cells including cardiac myocytes (Catterall et al., 1993; Dubel et al., 1992). Considering negative inotropic effects of L-type calcium channel blockers, therefore, discovering purely selective and potent small-molecule N-type calcium channel blockers (not yet available) could be a potential new therapeutic strategy to inhibit ventricular arrhythmias and improve the outcome in patients with HF. Fourth, thoracic epidural anesthesia or thoracic sympathectomy effectively reduces cardiac sympathetic activity, and suppresses ventricular arrhythmias in patients with HF (Bourke et al., 2010; Hofferberth et al., 2014; Schneider et al., 2013; Schwartz, 2014b; Vaseghi et al., 2014; Vaseghi et al., 2017). However, adverse complications of these procedures (including hyperhidrosis, Horner’s syndrome, and paresthesia) severely limit use of the procedures in patients with HF (Rathinam et al., 2008). Additionally, animal experimental studies and clinical trials has demonstrated the therapeutic effect of renal nerve denervation on ventricular arrhythmias (Bradfield et al., 2014; Evranost et al., 2016; Hopper et al., 2017; Huang et al., 2014; Jackson et al., 2017; Linz et al., 2013; Reddy and Miller, 2015; Remo et al., 2014), which should be a potential nonpharmacological candidate for the treatment of ventricular arrhythmias in HF.

3.3. Catheter ablation

Catheter ablation is a procedure that uses radiofrenquency energy to stop cardiac arrhythmias through scaring or destroying a small area of the heart. As the arrhythmic substrate, this small area of the heart usually has the functional or structural abnormality and causes cardiac arrhythmias. Following the development of cardiac mappings including activation mapping, pace mapping, and entrainment mapping, especially use of electroanatomical mapping system coupling with electrogram recordings and three-dimensional anatomical displays, catheter ablation is considered to be an effective treatment option for suppression of ventricular arrhythmias in HF when antiarrhythmic drugs are not tolerated or are not highly effective (Baher and Valderrabano, 2013; Kumar et al., 2016; Liang et al., 2015; Santangeli and Marchlinski, 2016; Santangeli et al., 2017). However, some concerns, including higher complication rates and limited in large academic centers with very experienced clinicians, exist in the use of catheter ablation (Baher and Valderrabano, 2013). A more detailed introduction and discussion of catheter ablation has been taken in other review papers (Baher and Valderrabano, 2013; Kumar et al., 2016; Liang et al., 2015; Santangeli and Marchlinski, 2016; Santangeli et al., 2017), which is beyond the scope of this review paper.

4. Conclusion

Although there have been remarkable advances in the cellular and molecular mechanisms responsible for ventricular arrhythmias in HF and related pharmacological and nonpharmacological therapeutics in the past few decades, the poor efficacy and potential adverse effects of current antiarrhythmic drugs influence clinical outcomes of patients with HF. Exploring the cellular and molecular bases of ventricular arrhythmias and discovering substrate-based antiarrhythmic drugs (such as small-molecule specific blockers of late-sodium-currents, late-calcium-currents, or N-type calcium channels) are crucial for improving prognosis of HF and reducing its mortality. Of course, novel anatomical and physiological imaging modalities including incorporation of all imaging techniques (such as CT, MRI, ultrasound, and electroanatomical mapping) and the proper use of catheter ablation as an adjunctive treatment also effectively suppress ventricular arrhythmias and reduce mortality and sudden cardiac death in HF.

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Table 1.

Potential substrates for ventricular arrhythmias in heart failure (HF)

	Alterations	
Ventricular structure and mechanics	**a.**	Ventricular scar
	b.	Ventricular hypertrophy
	c.	High ventricular filling pressure
	d.	Increases in cardiac preload and afterload
Ventricular metabolism	**a.**	Acidosis and increases of lysophosphoglycerides, adenosine, lactate, and carbon dioxide in the extracellular fluid
	b.	Increases of calcium, magnesium, sodium, and cyclic adenosine monophosphate in the intracellular fluid
	c.	Increase or decrease of extracellular potassium levels
Ventricular electrophysiology	**a.**	Prolongation of action potential duration
	b.	QT prolongation and dispersion
Neurohumoral substances	**a.**	Elevation of plasma epinephrine and norepinephrine
	b.	Cardiac sympathetic overactivation