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Effect of asymmetric dimethylarginine (ADMA) on heart failure development

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Abstract

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthases that limits nitric oxide bioavailability and can increase production of NOS derived reactive oxidative species. Increased plasma ADMA is a one of the strongest predictors of mortality in patients who have had a myocardial infarction or suffer from chronic left heart failure, and is also an independent risk factor for several other conditions that contribute to heart failure development, including hypertension, coronary artery disease/atherosclerosis, diabetes, and renal dysfunction. The enzyme responsible for ADMA degradation is dimethylarginine dimethylaminohydrolase-1 (DDAH1). DDAH1 plays an important role in maintaining nitric oxide bioavailability and preserving cardiovascular function in the failing heart. Here, we examine mechanisms of abnormal NO production in heart failure, with particular focus on the role of ADMA and DDAH1.

Keywords

Nitric oxide; Asymmetric dimethylarginine; dimethylarginine dimethylaminohydrolase-1; heart failure

Introduction

Chronic Heart failure (CHF) is a condition in which the left heart is not able to pump out sufficient oxygen-rich blood into circulation to meet the body's needs. The term "congestive heart failure" is often used interchangeably with "chronic left heart failure". The common clinical symptoms of CHF include shortness of breath (dyspnea), excessive fatigue or reduced exercise capacity and swelling (edema) in legs and feet etc (32,45). The common

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causes of CHF include prolonged high blood pressure (chronic hypertension), myocardial infarction (heart attack) after coronary artery disease, cardiac valve disease, idiopathic cardiomyopathy, myocarditis from inflammation, and congenital heart diseases etc (32,73). The prevalence of CHF patients is ~6.6 million adults in 2010, and it is projected that additional 3 million people will have CHF by 2030 (39). CHF is the leading cause of death in United States (83).

Nitric Oxide (NO) is an endogenously produced, locally acting gas that exerts multiple actions that help preserve cardiac function in the setting of CHF (17,47, 58,85). NO synthesis is catalyzed by a family of NO synthases (NOS), which use L-arginine as the substrate to produce NO and L-citrulline. In mammals, there are at least 3 NO synthases; endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). eNOS is most stongly expressed in vascular endothelial cells, while nNOS is predominant in neuronal cells and skeletal muscle, but both forms are expressed at lower levels in many cell types (17,47). iNOS is predominantly expressed in leukocytes under normal conditions, but it is also induced in various cells in response to inflammation or other stress signals. eNOS and nNOS produce NO in response to increased cytosolic Ca^{++} (Ca^{++}-dependent NOS), while iNOS is constitutively active (17,47). NO produced by eNOS, the major isoform in the endothelium, plays a critical role in vascular tone by diffusing into adjacent smooth muscle cells (17,48). NO activates soluble guanylate cyclase, promoting cGMP production, subsequent activation of cGMP dependent protein kinase or Protein Kinase G (PKG). PKG phosphorylates a number of important intracellular targets that cause smooth muscle relaxation and increased blood flow (17,33,48). During heart failure, coronary or systemic vasodilatation in response to agonists or shear stress are attenuated, in part due to decreased vascular NO bioavailability (20,22). NO-cGMP signaling also modulates other vessel related functions including angiogenesis, vascular endothelial cell growth/proliferation, platelet aggregation, and injury repair. Importantly, reduced NO bioavailability contributes to hypertension, coronary disease, atherosclerosis, diabetes, and renal dysfunction, a group of risk factors that promote or exacerbate CHF. NO production is regulated by substrate L-arginine availability (17), NOS protein content and quality, NOS cellular and subcellular distribution, tetrahydrobiopterin (BH4, an essential cofactor for the dimerization of NOS) availability (17), endogenous NOS inhibitors asymmetric dimethylarginine (ADMA) and N-monomethy L-arginine (L-NMMA) (59,77), and the enzyme activity of dimethylarginine dimethylaminohydrolase-1 (DDAH1) (Figure 1) (44,77). ADMA and L-NMMA attenuate NO production by all NOS isoforms (15,16). Here we will briefly review the role of ADMA and DDAH1 in regulating cardiovascular NO production and heart failure development.

NO/cGMP/PKG signaling and CHF development

In addition to the well-established role of NO-cGMP signaling in maintaining normal cardiovascular function, NO protects against cardiac remodeling and dysfunction under stress conditions such as aging (65), myocardial infarction, and pressure overload (58,85). For example, progressive cardiomyocyte hypertrophy, interstitial fibrosis, left ventricular dilation and dysfunction that develops in the surviving tissue after myocardial infarction, are exacerbated in eNOS KO mice as compared to wild type mice (85), while transgenic mice over-expressing eNOS are protected from myocardial infarct-induced left ventricular

remodeling, cardiac death, and the development of CHF (29,58,85). eNOS KO also was shown to exacerbate left ventricular dysfunction in response to increase of systemic pressure overload produced by aortic banding (58,84), while cardiomyocyte-restricted restoration of eNOS (over-expressing eNOS in eNOS KO mice) reversed the exacerbated aortic banding-induced ventricular remodeling in eNOS KO mice (13), indicating an important role of NO in maintaining cardiomyocyte function. Over-expression of eNOS also attenuated myocardial infarction induced compensatory hypertrophy and left ventricular failure in comparison to wild type mice (56). The protective effects of NOS signaling are largely attributed to cGMP production and activation of PKG, which targets several proteins involved in cardiac contractility, hypertrophy and remodeling.

Besides promoting cGMP production, NO modulates cardiovascular function by promoting post-translational modification of proteins via S-nitrosylation. For instance, S-nitrosylation of L-type calcium channels reduces ventricular arrhythmias and mortality in mice after myocardial infarction (12), while S-nitrosylation of the ryanodine receptor can reduce diastolic calcium leak (37). S-nitrosylation also regulates G-protein coupled receptor signaling (42) and the stability of PDE5 (107), an enzyme that degrades cGMP to exacerbate heart failure development (70). Thus, NOS influences cardiac signaling and adaptation to stress through both the NO-cGMP pathway and NO dependent S-nitrosylation.

While eNOS and nNOS activity are generally considered cardioprotective, iNOS expression can be detrimental (14,38,114). This is likely due to unmitigated production of NO and superoxides by iNOS uncoupling (6,111,114) resulting in peroxynitrite formation in the inflammatory setting of heart failure and resulting tissue damage (38,78,114). Excessive NO may also promote apoptosis (38) or cardiomyocyte dysfunction (14) through aberrant S-nitrosylation. In addition, under certain conditions, such as oxidative stress (117), when levels of the cofactor tetrahydrobiopterin is limited, or when bioavailability of L-arginine is insufficient, the normally protective effects of NOS signaling can be derailed by NOS “uncoupling”. Under optimal conditions, NOS bound to the co-factor tetrahydrobiopterin forms a homodimer and produces NO using L-arginine as the substrate. In absence of tetrahydrobiopterin, which may be limited under oxidative stress conditions, NOS becomes uncoupled, and NOS monomers produce superoxide rather than NO. We found that both iNOS and eNOS monomers were increased in failing hearts from wild type mice in response to TAC, and this was associated with increased myocardial superoxide production (114). Furthermore, iNOS gene deficiency or the selective iNOS inhibitor 1400W protected the heart against TAC-induced left ventricular failure and oxidative stress (114).

Because NO signaling is often impaired in CHF, strategies to promote cGMP production by pharmacological activation of guanylate cyclase (27,36) or blocking cGMP degradation using cGMP specific phosphodiesterase inhibitors are being examined as potential treatments for CHF (61,70,67,95). While promising results have been obtained through these strategies in animal models, success of these approaches in human trials has been mixed or unknown (11,66). Identification and targeting of NO/cGMP/PKG signal pathway may lead to new treatments for CHF.

Cellular and subcellular localization of eNOS and DDAH1

Because NO diffusion distance is quite limited, the cellular and subcellular distribution of eNOS are important for NO signaling. eNOS is predominantly expressed in vascular endothelial cells, so that the level of eNOS expression in a particular tissue is often related to its vascularity. In the heart, eNOS is not only expressed in vascular endothelial cells, but is also expressed on sarcolemma of cardiomyocytes (17,34). In vascular endothelial cells, eNOS is mainly localized to the plasma membrane and Golgi complexes (35,69,89). Interestingly, the activity of eNOS located at cell membrane is higher than eNOS distributed in Golgi, nucleus and mitochondria (50,55,89,116). The plasma membrane localization of eNOS facilitates diffusion of NO into adjacent smooth muscle cells to regulate vascular tone. In cardiomyocytes, eNOS is predominantly localized to caveolae on the sarcolemma, and also found on Golgi complexes(7,34,114), while nNOS is localized to the sarcoplasmic reticulum. DDAH1, the critical enzyme for ADMA and L-NMMA degradation, is highly abundant in tissues with high nNOS expression such as brain, in tissue removing ADMA (such as kidney, and liver), and in tissues with high eNOS expression (such as lung) (43,101). At least in the heart, the cellular distribution of DDAH1 is similar to eNOS (20). The subcellular distribution of DDAH1 in vascular endothelial cells is not clear, but the subcellular distribution of DDAH1 in cardiomyocytes is similar to subcellular localization of eNOS (20). The similar cellular and subcellular distribution of DDAH1 and eNOS in the heart may facilitate compartmentalized NO production at the plasma membrane of endothelial cells and cardiomyocytes, and also improve overall cardiac NO bioavailability.

Effect of ADMA and L-NMMA on CHF and the common causes of CHF

Endogenous NOS inhibitors ADMA and L-NMMA compete with L-arginine for NOS binding to attenuate NO production (15). As ADMA is more abundant than L-NMMA, most of the studies have focused on the physiological or pathological effects of ADMA in various biological or clinical conditions. By preventing L-arginine binding to NOS, ADMA not only reduces NO formation, but can also promote superoxide formation, similar to L-arginine depletion.

Importantly, ADMA levels are strongly associated with CHF (Figure 2) (31,40,99,112) and the common causes for CHF (Figure 3). For examples, accumulation of ADMA occurs in hypertension (92), coronary disease (8,76,88,91), cardiac valve disease (2), idiopathic cardiomyopathy (3), congenital heart diseases (103), renal failure (54), diabetes (4,67), and atrial fibrillation (18,19) (Figure 3). Elevated plasma ADMA levels are associated with an increased risk for developing angina pectoris, myocardial infarction or cardiac death (9,10). Plasma ADMA level is the strongest predictor of mortality in patients after myocardial infarction (76,88), and a strong and independent predictor of all-cause mortality in the community (9). In addition, studies have shown that infusion of ADMA results in reduced endothelium-dependent coronary vasodilation in pacing induced heart failure dogs (23) and in mice (44) a decrease of cardiac output in normal human subjects (1), and hypertension in mice (44,63). Together, chronic ADMA accumulation may either exacerbate CHF development directly or exacerbate CHF development through increase of cardiovascular

risk factors such as hypertension, diabetes, atherosclerosis, coronary disease and renal failue as summarized in Figure 3.

Because plasma levels of L-arginine far exceed the levels of plasma ADMA, it has been suggested that ADMA may be a feature of cardiovascular diseases, but does not reach sufficient levels to compete with L-arginine and inhibit NOS. However, ADMA appears to accumulate within cells to a concentration sufficient to impair NOS activity, despite the higher concentration of L-arginine relative to ADMA in plasma (10,15). In addition, chronic infusion of ADMA was reported to increase vascular angiotensin-converting enzyme, oxidative stress, and vessel lesions, suggesting that ADMA can cause vessel injury at least partially through modulating oxidative stress (93). Interestingly, this study also reported that chronic ADMA infusion caused similar increases of vascular angiotensin-converting enzyme, oxidative stress and vessel lesions in eNOS deficient and wild type mice, suggesting that ADMA may exert detrimental effects beyond its disruption of eNOS derived NO production. At the present time, it is unclear whether chronic ADMA accumulation observed in CHF can actually cause or exacerbate the development of myocardial dysfunction or CHF.

While the detailed molecular mechanism for increased ADMA and L-NMMA in various pathological conditions is not clear, there is some evidence that accumulation of ADMA and L-NMMA may result from depressed DDAH1 expression or activity, either through loss-of-function polymorphisms of the DDAH1 gene (104), reduced DDAH1 transcript expression (21), or post-translational modifications such as oxidation of DDAH1 protein. For example, Valkonen et al identified a mutation of the DDAH1 gene that is associated with high plasma ADMA levels and conveys an increased risk for coronary heart disease and an increased prevalence of hypertension (104). DDAH activity is also depressed by oxidized LDL and TNFα (51), high levels of homocysteine in endothelial cells (91), and high plasma glucose in diabetic rats (67). In addition, our previous study showed that mechanical unloading by left ventricular assistant device caused significant decreases of a group of pro-inflammatory cytokines and increase of myocardial DDAH1 mRNA and protein content in left ventricular tissue from patients with severe CHF (21), suggesting that mechanical stresses regulate myocardial DDAH1 protein expression in the failing heart.

ADMA and L-NMMA production and removal

Protein methylation plays an important role in many cellular functions and occurs constitutively in cells. The production of ADMA and L-NMMA is the result of proteolysis of proteins containing methylated arginines (74,81,90). L-NMMA is formed when protein-incorporated L-arginine is methylated by the enzymes protein arginine methyltransferases type I (PRMT-I) or type-II (PRMT-II) (74,81). PRMT-I can subsequently methylate L-NMMA, resulting in the formation of ADMA, whereas PRMT-II can methylate L-NMMA into symmetric dimethylarginine (SDMA) (74,81). Methylated arginines are released as unbound forms in the cytosol then transported into the circulation via system y+-carriers of the cationic amino acid transporter (CAT) family. Similar to L-arginine, ADMA, L-NMMA and SDMA can be taken up by other cells using CAT. Both ADMA and L-NMMA directly compete with L-arginine for the active site of NOS to attenuate NO production. SDMA does

not directly inhibit NOS activity, but SDMA could attenuate NOS function indirectly by inhibition of the CAT (24). The strong association between increased ADMA levels and CHF suggests ADMA production may be increased or its removal may be decreased under these conditions. One possible source of increased ADMA is increased protein degradation by autophagy or proteasome activity during tissue remodeling and inflammation associated with cardiovascular diseases. Interestingly, inhibition of proteasome activity in cultured cells reduced free levels of ADMA and SDMA, while inhibition of autophagy only reduced ADMA (100) Both autophagy and proteasome activity are up-regulated during various phases of CHF (106), while protein synthesis is often increased as well, so that protein turnover and subsequent production of ADMA and L-NMMA may also be elevated. However, the contribution and significance of these pathways to ADMA production in CHF is not known.

Once ADMA and L-NMMA are released by proteolysis, they are eliminated from the body in part through renal excretion (1). As ADMA was first isolated from human urine by Kakimoto and Akazawa in 1970 (59), renal excretion was initially recognized as the major route for ADMA elimination. However, a study from McDermott subsequently showed that the urinary recovery of L-NMMA and ADMA following intravenous injection in rabbits was only 0.14% and 5.1%, respectively, indicating that both L-NMMA and ADMA undergo extensive metabolism (75). Ogawa et al further identified an enzyme termed dimethylarginine dimethylaminohydrolase (DDAH, it is currently named as DDAH1) that catalyzes hydrolysis of L-NMMA and ADMA into L–citrulline and mono- or dimethylamine (77). A second DDAH isoform (DDAH2) was reported in 1999 (62). While early studies suggested that both DDAH1 and DDAH2 are effective in degrading ADMA and L-NMMA, we have demonstrated that DDAH1 is the essential or sole enzyme responsible for ADMA degradation in mice and in cultured human endothelial cells (44).

The critical role of DDAH1 in ADMA degradation

As stated above, two DDAH isoforms have been reported. Previous existing concepts regarding tissue or cell specific DDAH1 biology and their function in regulating NO production in various tissues are based on the reports that DDAH1 and DDAH2 have comparable activities for degrading ADMA and L-NMMA (62), as well as the report that DDAH1 is minimally expressed in the heart (62,100), vessels (62) and vascular endothelial cells (5). Accordingly, it was originally accepted that DDAH2 plays the major role in regulating ADMA and L-NMMA levels in the heart and vessels, while DDAH1 plays the major role in degrading ADMA and L-NMMA in neuronal tissues. However, we observed that DDAH activity was totally abolished in all tissues obtained from global DDAH1 deficient mice while the expression of DDAH2 was unaffected in these tissues (43). In other words, tissues obtained from global DDAH1 KO mice are unable to degrade ADMA or NMMA even though DDAH2 expression is not affected (43). Consistent with our findings, Dr. Leiper *et al.* also demonstrated that DDAH activity was reduced ~50% in tissues obtained from heterozygous DDAH1 KO mice (63). Furthermore, selective gene silencing of DDAH1 (but not DDAH2) caused accumulation of ADMA and decreased NO production in cultured human endothelial cells (43), while over-expression of DDAH1 (but not DDAH2) decreased ADMA content in cultured human endothelial cells (113). These findings clearly

indicate that DDAH1 is the critical enzyme for ADMA degradation, while DDAH2 has no detectable role in ADMA degradation in both mouse tissues and human cells.

The important role of DDAH1 in cardiovascular function

DDAH1 plays an important role in regulating cardiovascular function and risk factors of CHF by degrading endogenous NOS inhibitors ADMA and L-NMMA. Thus, DDAH1 gene deficiency causes increases of plasma and tissue ADMA and L-NMMA, which is associated with reduced NO production, moderate hypertension, and endothelial dysfunction (43,44,63). DDAH1 gene deficiency also limits angiogenesis and impairs vascular injury repair (30,113,115). Conversely, over-expression of DDAH1 results in decreases of plasma and tissue ADMA levels, which was associated decrease of systemic blood pressure (28), increase of insulin sensitivity (94), increase of angiogenesis (53,113,115), reduced high fat diet induced atherosclerosis (52,108) and graft coronary artery disease (98). These findings indicate that endogenous ADMA levels are sufficient to alter vascular tone and other tissue functions, and suggest that elevating DDAH1 activity to eliminate ADMA could be a promising strategy for restoring NOS function and increasing NO bioavailability in CHF and other cardiovascular diseases.

While the recent studies clearly show DDAH1 plays the critical role for ADMA and L-NMMA degradation, the significance of endothelial DDAH1 in regulating cardiovascular NO signaling is not totally clear. Using the Tie-2 Cre system, we found that endothelial specific DDAH1 gene deletion caused significant decreases of DDAH1 in vascular tissues, increased tissue and plasma ADMA, reduced acetylcholine induced NO production and vessel dilatation, and resulted in systemic hypertension (43,44), abnormal angiogenesis, and impaired endothelial injury repair (113,115). However, using a similar Tie-2 Cre system, a new endothelial specific DDAH1 strain was shown to have no major effect on systemic ADMA content (30), but significantly attenuated angiogenesis (30). While endothelial specific DDAH1 gene deletion using Tie-2 Cre system attenuated endothelial injury repairs and angiogenesis in both mouse strains, the effect of endothelial DDAH1 gene deletion on systemic blood ADMA was different in these mouse strains. Unfortunately, the causes of the discrepancy of endothelial DDAH1 on systemic blood ADMA between these two endothelial DDAH1 gene deficient strains are not clear at this point.

An important role of kidneys in ADMA metabolism

Kidneys are the organs with highest DDAH1 expression and play an important role in regulating systemic ADMA and L-NMMA. It was reported that less than 20% ADMA was excreted via urine in humans, indicating that over 80% of ADMA is metabolized by DDAH (1). Thus, it is generally believed that ADMA and L-NMMA are eliminated principally by DDAH with a small contribution from renal excretion at least in human. However, gene deletion of DDAH1 (DDAH1 knockout mice has no detectable tissue DDAH activity) causes only ~2 fold increase of plasma ADMA and L-NMMA in mice under control conditions (44), while plasma ADMA and L-NMMA generally increases over 4 fold (increases up to 10 fold) in patients with severe renal failure (10,54). While the dramatic increase of plasma ADMA and L-NMMA in renal failure is likely a combined result of diminished renal

ADMA and L-NMMA excretion and decreased degradation by renal DDAH1, these findings clearly indicate that kidneys play a greater role in ADMA and L-NMMA elimination than previously thought. In addition, these data suggest that kidneys may be able to dramatically increase excretion of ADMA and L-NMMA when ADMA and L-NMMA are overloaded in response to DDAH1 dysfunction. Thus, the important role of the kidneys in ADMA and L-NMMA metabolism under stress conditions may have been underestimated by the field.

ADMA enhances NOS-derived O_2^- and peroxynitrite ($ONOO^-$)

Although the most obvious consequence of increased levels of ADMA and L-NMMA is to inhibit NO production, recent reports indicate that the endogenous NOS inhibitors may also cause NOS to generate O_2^- and peroxynitrite rather than NO (Figure 1). Normally, NOS transfers electrons from NADPH, via the flavins FAD and FMN in the carboxy-terminal reductase domain, to the heme in the amino-terminal oxygenase domain, where the substrate L-arginine is oxidized to L-citrulline and NO. The flow of electrons within NOS is normally tightly regulated. However, when this flow is disrupted, oxygen reduction and NO generation can become uncoupled so that O_2^- is generated by the oxygenase domain. This uncoupling can occur when NOS is exposed to oxidant stress (including peroxynitrite), when it is deficient in the reducing cofactor BH4 (25,60), or when it is deprived of its substrate L-arginine (110). BH4 is required for iNOS dimerization (6,26) and stabilizes the dimeric forms of eNOS, nNOS and iNOS (6). Thus, BH4 depletion (or oxidation of BH4 to BH2) can induce NOS-derived O_2^- generation (6,25,96). Deprivation of the substrate L-arginine can also induce NOS to generate O_2^- and $ONOO^-$ (110,111,117). Similar to substrate deficiency, several *in vitro* studies have demonstrated that addition of ADMA or L-NMMA caused O_2^- generation by purified NOS protein (16,67,78), and also in cultured human endothelial cells (16), isolated arterioles from rat gracilis muscle (100), and in a murine lung epithelial cell line LA-4 (109). In vitro studies have demonstrated that the NOS inhibitor N-monomethyl-L-arginine (L-NMMA) is also capable of inducing NOS uncoupling through multiple mechanisms such as heme loss (78). Importantly, elevated superoxide in cardiomyocytes or endothelial cells can interact with and scavenge NO before it can activate guanylate cyclase to produce cGMP or be utilized for S-nitrosylation, thereby further impairing NO signaling. Reduced NO bioavailability or increased ROS is also known to increase PDE5 activity (70) partially through attenuating PDE5 nitrosylation (107), suggesting further indirect effects of NOS uncoupling on reducing cGMP signaling. ADMA inhibition of NOS, through inhibition of NO production as well as NOS uncoupling and superoxide production, thus acts as a double edged sword in endothelial and cardiomyocyte pathophysiology. Importantly, administration of tetrahydrobiopterin, which prevents NOS uncoupling, can significantly attenuate ROS production, pressure overload induced cardiac hypertrophy and heart failure, indicating that the loss of NO production, as well as increased ROS production that results from NOS uncoupling contributes to CHF (17,57). It is possible that strategies to reduce ADMA levels in conjunction with increasing BH4 may further alleviate NOS dysfunction during CHF. Therefore, identifying methods to increase DDAH1 activity and reduce ADMA levels may be clinically important.

Regulation of DDAH1 expression by farnesoid X receptors (FXR) agonists and ursodeoxycholic acid (UDCA)

UDCA is a major component of bear bile, which has been used for thousands of years in traditional Chinese medicine to treat a variety of illnesses. Endogenous bile acids are produced in the liver and are essential for cholesterol catabolism and intestinal lipid emulsification. In addition to their role as detergents, bile acids play an important role in maintaining lipid and glucose homeostasis through activation of FXR (102) and pregnane X receptors (46). Currently, UDCA is approved by the FDA for treatment of primary biliary cirrhosis (97) and other liver diseases. Importantly, a recent report demonstrated that UDCA, as well as the FXR agonist GW4064 dose dependently increased DDAH1 expression in the liver and lowered plasma ADMA levels through an FXR response element located within the first exon of the DDAH1 gene (41). A separate study by a different group also demonstrated that activation of FXR with GW4064 increased DDAH1 gene expression in the liver and kidney, and decreased plasma ADMA (64). Interestingly, 6 weeks' UDCA therapy was found to improve endothelium-dependent vasodilatation and arterial blood flow in patients with CHF under conditions of impaired nitric oxide production (91). In addition, a randomized, placebo-controlled clinical trial demonstrated that UDCA significantly improved peak post-ischemic blood flow in the arm (105). It will be important to find out if increased endothelial DDAH1 expression and/or reduction of ADMA levels played a role in the beneficial effects of UDCA observed in these clinical studies.

Bile acids, GW4064, or hepatic expression of constitutively active FXR, have previously been found to significantly lower plasma triglyceride, cholesterol and glucose levels (71,72). Interestingly, genetic disruption of eNOS or nNOS has also been shown to alter lipid metabolism, resulting in increased fat deposition in the liver (86,87). Similarly, FXR gene deletion increased plasma lipid levels (80). While the effects of UDCA on cardiomyocyte DDAH1 expression and NO signaling are unknown, there is evidence that UDCA can attenuate ER stress (79), and apoptosis, which are commonly observed in CHF (68,106). UDCA was also shown to protect against apoptosis in a myocardial ischemia reperfusion injury model (82). These findings suggest UDCA or other FXR agonists could provide a novel approach to increase DDAH1 expression to restore NO signaling in cardiovascular diseases. It will therefore be important to find out whether UDCA activation of FXR induces DDAH1 gene expression in the cardiovascular system or whether this effect is restricted to liver and kidney.

Summary

The current scientific literature in the field indicates that the NO/cGMP/PKG signaling pathway plays an important role in attenuating CHF development and/or progression through modulating cardiac perfusion, myocardial contractility and myocardial energy efficiency. ADMA attenuates vascular NO bioavailability in the cardiovascular system, and DDAH1 plays the major role in ADMA degradation to maintain cardiovascular NO/cGMP/PKG signaling. Increased plasma ADMA is one of the strongest predictors of mortality in patients who have had a myocardial infarction or suffer from CHF, and is also

an independent risk factor for several other conditions that contribute to CHF development, including hypertension, coronary artery disease/atherosclerosis, diabetes, and renal dysfunction. Together these findings suggest that increasing or maintaining normal DDAH1 expression and/or activity could be an important therapeutic target for improving NO bioavailability in CHF and other cardiovascular diseases.

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Abbreviations

CHF	chronic Heart failure
ADMA	Asymmetric dimethylarginine
BH4	tetrahydrobiopterin
DDAH1	dimethylarginine dimethylaminohydrolase 1
PRMT1	type 1 protein arginine N-methyltransferase
NOS	nitric oxide synthesis
iNOS	inducible NOS
eNOS	endothelial NOS
PKG	protein kinase G
ROS	reactive oxygen species
KO	knockout
L-NMMA	N-monomethy L-arginine
SDMA	symmetric dimethylarginine
CAT	cationic amino acid transporter
FXR	farnesoid X receptors
UDCA	ursodeoxycholic acid

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Highlights

- ADMA may exacerbate heart failure development directly.
- ADMA may exacerbate heart failure through increase of cardiovascular risk factors.
- DDAH1 plays a critical role in ADMA degradation.

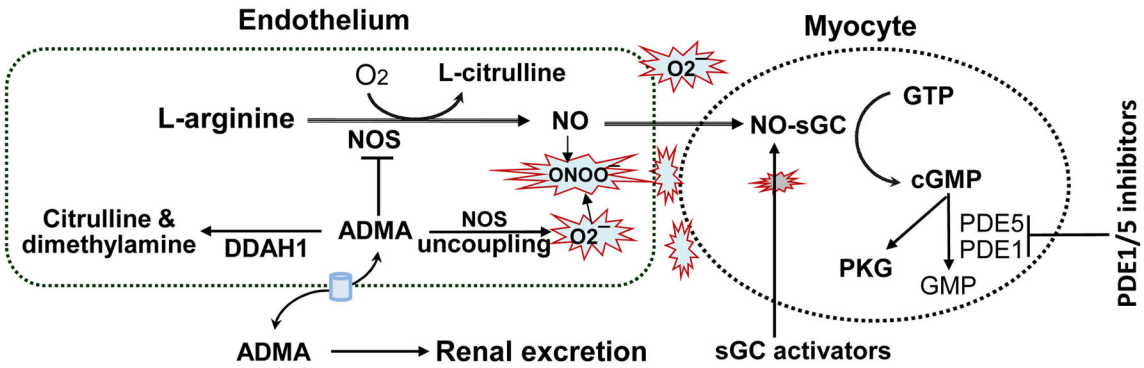

Figure 1.

ADMA attenuates nitric oxide synthase (NOS)-induced NO/cGMP/PKG signaling and increases NOS derived superoxide anion production in vascular endothelial cells.

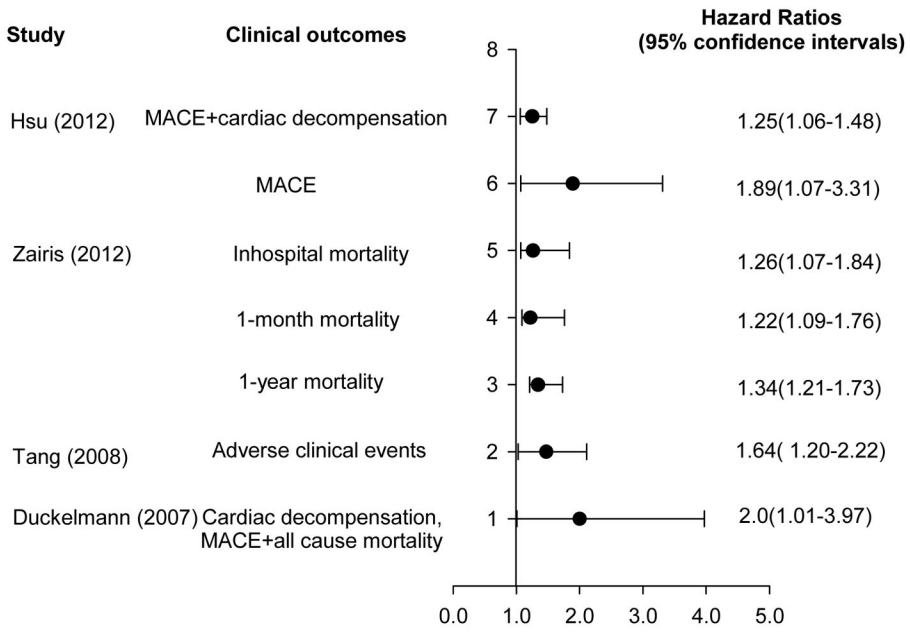

Figure 2.

ADMA levels are independent predictors of cardiovascular events in patients with congestive heart failure and the Major Adverse Cardiac Events (MACE).

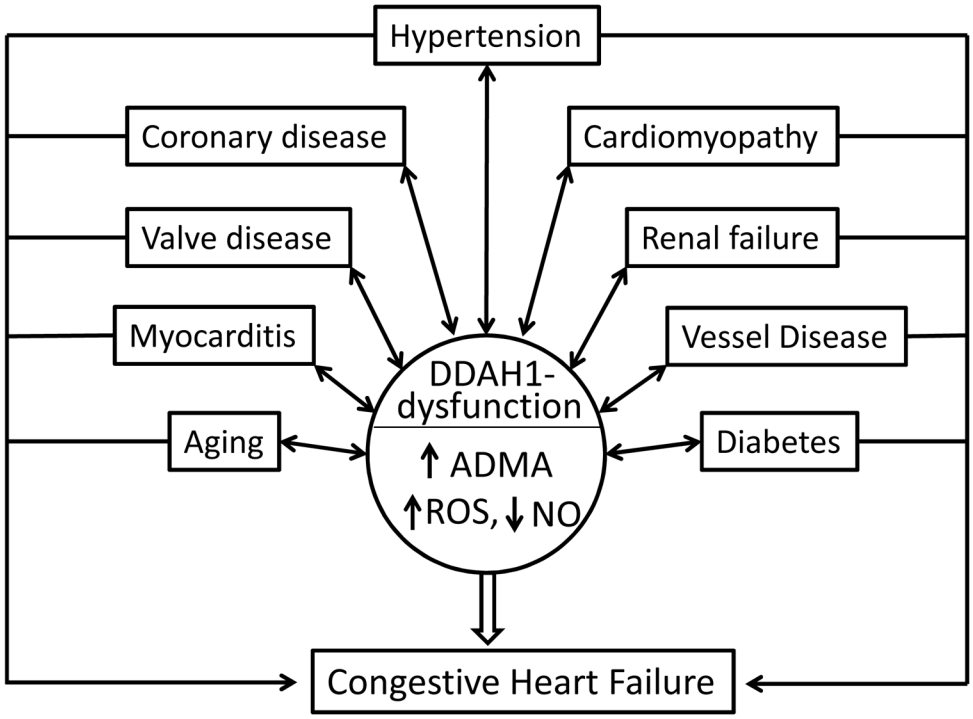

Figure 3.

The proposed mechanism of DDAH1 dysfunction and accumulation of ADMA on the development of congestive heart failure through modulating various cardiovascular risk factors.