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The Historic Pathophysiologic Journey of Heart Failure Management: Targeting Oxidative Stress with the Antioxidant Glutathione. Are Antioxidants Another “Arrow” in the Quiver of Heart Failure Therapy?

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The Historic Pathophysiologic Journey of Heart Failure Management: Targeting Oxidative Stress with the Antioxidant Glutathione. Are Antioxidants Another "Arrow" in the Quiver of Heart Failure Therapy?

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Abstract: Early treatments of heart failure (HF) were directed toward management of fluid overload and providing inotropic support. Now, management of HF is multifaceted. Many of these treatments were established from outcomes of clinical trials. Each study has broadened our understanding of HF pathophysiology. The current regimens now include medications directed against the renin-aldosterone, angiotensin system (RAAS), the sympathetic system, and the natriuretic system. Recently, the sodium-glucose transport-2 inhibitors (SGLT2i) that were initially given to treat Type 2 diabetes are now recognized as being effective to treat HF. Since this effect was also beneficial in non-diabetic individuals, it prompted investigations to determine another mechanism of action (MOA) apart from its primary one that inhibits renal glucose reuptake. It led to the discovery of its anti-inflammatory property. This is notable since HF is associated with oxidative stress (OS) that is the result of excessive inflammation. It has highlighted the goal of reducing OS with an antioxidant as another target in HF treatment. Glutathione (GSH) is a well-known anti-inflammatory agent. Studies with its use in HF patients could determine the role of antioxidants in HF by reducing OS. A novel nano-product, the glutathione-cyclodextrin (G-C) complex will be presented that therapeutically delivers GSH. Studies using the G-C complex should determine the efficacy of GSH to suppress OS. If those studies are confirmatory, antioxidants could be another "arrow" in the quiver of HF management.

Keywords: Renin-angiotensin-aldosterone system; sympathetic system; natriuretic system; oxidative stress; antioxidants; glutathione; cyclodextrin

1. Introduction

" A man cannot become a competent surgeon without the full knowledge of human anatomy and physiology, and the physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practicing a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which." Sir William Osler (1849-1919)

To echo Sir Osler, in order to optimally treat a patient, one must not only know what, but why. The "what" is the disease, and the "why" is the underlying pathophysiology that creates the disease. In disease progression, pathophysiology is often a maladaptive physiologic response to an initial acute trigger or a chronic insult. Avoiding or managing a pathophysiologic process has the advantage of preventing rather than reversing disease pathology. The treatment of heart failure (HF) is an example of this premise. In addition of the historical use of furosemide and digoxin, we now manage HF by targeting the adverse consequences of persistent stimulation of the renin-antiogensin-aldosterone (RAAS) system, the sympathetic system and the natriuretic system. Evidence will be

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presented that reducing oxidative stress (OS) is another therapeutic target in HF management. Addressing this may be accomplished by administering a potent antioxidant, glutathione.

2. Historical Evolution of Heart Failure Treatments

2.1. Heart Failure Management from the Era of Diuretic and Digoxin Therapy

Initially (since the 1780s) heart failure was only managed with the inotrope, digitalis, and its refined derivative, digoxin. A significant advancement in care did not arrive until the discovery of loop diuretics (eg. furosemide) in the 1960s to treat volume overload. Interestingly, digoxin was so well excepted as a cornerstone in HF treatment since for centuries, that its clinical efficacy was not objectively studied until 1997. Now digoxin is no longer the drug of choice for chronic systolic heart failure, that is, heart failure with reduced ejection fraction (HFrEF). Instead, we treat HFrEF with a combination of carvedilol (a β-blocker), enalapril, (an angiotensin converting-enzyme inhibitor (ACEI), spironolactone (an aldosterone inhibitor), sacubitril, (a neprilysin inhibitor that is combined with an angiotensin receptor blocker (ARB), and now dapagliflozin (a sodium-glucose transport-2 inhibitor (SGLT-2i). What prompted the transition from digoxin to the current therapies? First, the outcomes of prospective clinical trials, second the better understanding of the pathophysiology of HF (which includes recognizing that inotropic therapy (ie. with milrinone) in chronic HF can be detrimental) and finally, accepting the inherent narrow therapeutic window of, and the many drug-drug interactions with, digoxin [1,2]. Now, HF management is more complex but also more effective.

2.2. Functional Categorization of Heart Failure

There are three functional categories of heart failure (HF), heart failure with reduced ejection fraction (HFrEF), HF with preserved EF (HFpEF) and the intermediate HF with mildly reduced EF (HFmrEF). EF is calculated as the percentage of the stroke volume divided by the end-diastolic volume. The EF respectively are ≤40, ≥50, and 41-49 [3].

3. The Influence of Clinical Trials in Heart Failure Management

3.1. Beta-Blocker Therapy – the MDPIT Trial

Therapeutic goals of HF treatment include reducing morbidity (especially those requiring hospitalization) and decreasing mortality, that is, to confer a better quality and duration of life. Current treatments are directed by the result of the outcomes of prospective clinical trials. An early study was the Multicenter Diltiazem Post-infarction trial (MDPIT) in 1988 [4]. Its proposed outcome was of a decreased post-infarction mortality with diltiazem that proved not to be the result. However a post-hoc analysis showed decreased mortality in a subset of individuals on a β-blocker [5]. Counterintuitively, this benefit was greater in lower EF. Eventually it was determined that sympathetic stimulation is adaptive acutely but maladaptive when sustained chronically [6]. Now metoprolol, bisoprolol, and carvedilol are mainstays in chronic HFrEF therapy.

3.2. Digoxin vs Vasodilator and Angiotensin Converting Enzyme Inhibitor (ACEI) therapy – the DIG Study and VHeFT Trials

In 1986, the results of the Veteran's Heart Failure trial (V-HeFT) was published that presented evidence of the reduction of morbidity and mortality of veterans having HFrEF with vasodilator therapy that reduced afterload (with hydralazine) and preload (with a nitrate) [7]. A subsequent study V-HeFT-II in 1991 used the newly approved ACEI, enalapril, that provided vasodilatation plus angiotensin inhibition [8]. Enalapril further decreased mortality over the vasodilators used in the Ve-HeFT I trial. It demonstrated the added benefit of angiotensin inhibition over vasodilator therapy [9]. This was in contrast to the outcome of the Digitalis Investigation Group (DIG) that noted a decrease in hospitalization rate but not mortality [10]. A subsequent post-hoc analysis of the DIG study for those receiving a low digoxin dose showed a decrease in short-term 1 year mortality when added to

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a diuretic and an ACEI [11]. This highlighted the narrow dosing range of digoxin for its optimal effect [12,13]. The detrimental outcome of patients in the milrinone trial further supported the negative effect of targeted inotropic support in chronic HF [1].

3.3. Aldosterone Antagonist Therapy – the RALES Study

The effectiveness of spironolactone, an aldosterone antagonist, when added to an ACEI and a loop diuretic for severe HFrEF was reported in the RALES study [14]. It completed the clinical evidence on the efficacy of HF treatments directed against the initial compensatory stimulation of the renin-angiotensin-aldosterone system (RAAS) and of the sympathetic system [15–23]. The use of a newer, non-mineralocorticoid, aldosterone receptor antagonist, finerenone, has advantages over spironolactone in having a better side effect profile. It is non-steroidal and does not cause gynecomastia and causes less hyperkalemia [24].

3.4. Natriuretic Peptide Therapy

Natriuretic peptide was first identified in 1983. In 1988, the B-type natriuretic peptide (BNP) was discovered and was found to be present in high concentration in cardiac tissues, particularly in the ventricles [25]. A high level of BNP was subsequently associated with HF and is used in its diagnosis and management, particularly with acute HF [26,27]. Similar to the disappointing outcome of the inotrope milrinone in the treatment of HF, the use of a recombinant human BNP, nesiritide, showed detrimental results. The initial enthusiasm of its use in 2000 until its eventual withdrawal in 2018 was reviewed [28].

3.5. Neprelysin Inhibition Therapy – the PARADIGM-HF Study

The activity of natriuretic peptides in HF is complex and nuanced. Rather than giving a therapeutic dose of NP as nesiritide, a physiologic approach of inhibiting degradation of endogenous NP with sacubitril, a neprilysin inhibitor, was determined to be effective in treating chronic HF with some limitations [29]. Its limitations include that it 1), increases the concentrations of angiotensin II and endothelin I that needs it to be combined with an ACEI or ARB (resulting in the combination angiotensin receptor-blocker/neprilysin inhibitor (ARNI) medication known as entresto), 2) is contraindicated in New York Heart Association (NYHA) class IV HF, and 3) is not superior to ACEI/ARB post-MI [30–32].

3.6. Sodium-Glucose Transporter -2 Inhibitors, "giflozin" Therapy – the EMPEROR, DAPA, and DELIVER Trials

Sodium-glucose transporter -2 inhibitors (SGLT2i) are used to treat type 2 diabetes by inhibition the renal reuptake of glucose in the proximal tubules. In addition to the glucose lowering effect, the SGLT2i have other clinical benefits [33]. It was found in the EMPA-REG OUTCOME trial to reduce major cardiovascular events (myocardial infarction, stroke) by 14%, all-cause mortality by 32%, cardiovascular death by 37%, hospitalization due to HF by 35%, and worsening diabetic nephropathy by 39%. The cardiorenal benefits were later found to be present in non-diabetic individuals [34]. This resulted in the concept of a multifaceted mechanism of action (MOA) of SGLT2i. These include diuresis/natriuresis, blood pressure reduction, increasing erythropoietin levels, improved cardiac energy metabolism, inflammation reduction, inhibition of the sympathetic nervous system, prevention of fibrosis and adverse cardiac remodeling, prevention of ischemia/reperfusion injury, prevention of dysregulation of the cardiac ion homeostasis, inhibition of SGLT2i in the heart, reduction of hyperuricemia, increasing autophagy and lysosomal degradation, decreasing epicardial fat mass, increasing circulating pro-vascular progenitor cells, decreasing oxidative stress (OS), and improving vascular function [34–36]. Of these MOA, there is an interrelationship between OS and the adverse results of inflammation, hyperuricemia, ischemia/reperfusion injury, and cardiac remodeling through fibrosis [37]. The key role of OS and inflammation was highlighted by Pabel et al. [38].

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Focusing on the cardiovascular benefit of SGLT2i, research evidence has demonstrated improved outcomes in HF. Significantly, not only in HFrEF but also in HFpEF [39]. The primary management of HFpEF is now with SGLT2i per the DELIVER, DAPA-HF, and EMPEROR-Preserved trial results plus selective use of ARNI for individuals with elevated BNP or MRA for those with EF near 50% [40]. A closely titrated loop diuretic is also indicated. The use of SGLT2i offers treatment of HF beyond volume and neurohormonal management [39]. Compared with HFrEF, the cause and pathophysiology of HFpEF is more complex. The former is usually the result of acute myocardial damage and the latter the result of the consequences of multiple risk factors and phenotypes. HFpEF risk factors include advanced age, HTN, DM, obesity, CKD, CAD, a-fib, and chronotropic incompetence [39,40]. The unanswered question is how much does OS and the antioxidant property of SGLT2i affect the pathophysiology of HF? [34,36,38,41,42].

4. Future Prospect of Antioxidants in HF Therapy

The influence of OS and inflammation in the pathophysiology of chronic HF has been reviewed [43]. Aimo et al. described the influence of mitochondrial dysfunction that leads to generation of reactive oxygen species (ROS) and reactive nitrogen species, that in turn, triggers the further ROS generation in the cytosol. They further outline influence of the resultant OS on cardiac function and remodeling, that is: 1) altered Ca^{2+} homeostasis and contractile function, 2) stimulation of cardiomyocyte hypertrophy, 3) induction of cardiomyocyte apoptosis, 4) promotion of fibrosis, and 5) activation or hampering of the inflammatory response. Notably, HF is characterized by a systemic inflammatory state, as reflected by the high levels of cytokines such as tumor necrosis factor alpha and interleukin-6. Furthermore, their higher level correlates with a higher NYHA classification and lower EF. Another cytokine (transforming growth factor -beta) that is released under OS suppresses glutathione activity and facilitates ROS-mediated fibrosis in the progression of HF [43]. The complex progression of both HFr EF and HFpEF that is driven by inflammation from innate and adaptive immunity is diagrammatically presented by Aimo et al. [43]. OS and inflammation appear to be the primary triggers of cardiac dysfunction in HFpEF. In addition, many co-morbid risk factors of HF (diabetes, obesity, advanced age, hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea, rheumatic diseases, and chronic kidney desease) are associated with OS [43]. Unfortunately, as of now, clinical trials with antioxidants have been disappointing. Among the antioxidants used were vitamin E and C, and coenzyme Q. The clinical outcomes may reflect the inability of those antioxidants to achieve therapeutic antioxidant efficacy either due to their inadequate absorption, metabolism, or intrinsic weakness. A monoclonal antibody, canakinumab, that is directed against IL-1β, shows some promise but has a prohibitive cost and causes immunosuppression [44].

4.1. SGLT2i vs GSH Antioxidant Therapy

The presumptive antioxidant property of SGLT2i appear to provide an answer by addressing the effects of OS and inflammation inherent in the pathophysiology of chronic HF for both HFrEF and HFpEF [42]. The only dilemma is that they are coupled to the primary MOA that produces glucosuria in the management of type 2 diabetes. An ideal treatment would be with a medication that specifically addresses OS and its associated inflammation, and that is cost-effective for long-term chronic HF management. GSH may be that medication [44–46]. None of the past studies have used GSH [16]. Obstacles to its use has been the lack of an effective delivery system that can overcome the current poor bioavailability of oral GSH and the cost and inconvenience of intravenous (IV) GSH [47].

4.2. Glutathione-Cyclodextrin Therapy

A novel nano-product has been developed that delivers GSH transdermally by sequestering it in γ-cyclodextrin to produce the GSH-cyclodextrin (G-C) complex [46]. There is evidence that the complex can effectively increase GSH levels and counter OS [48]. It avoids the problems of oral and

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IV delivery and the need for enzymatic conversion of N-acetyl cysteine (NAC) into GSH [49]. The complex therapeutically delivers the powerful antioxidant, GSH, and should encourage studies to determine its efficacy to counter OS and HF [45,46]. Unlike SGLT2i, it is uncoupled from other therapeutic actions and can specifically determine the role of OS in HF progression. If these studies support its efficacy, antioxidant therapies would provide another approach to HF management beyond countering the detrimental effects resulting from stimulation of the RAAS, sympathetic, and natriuretic peptide systems. Significantly, the G-C complex is a currently available non-prescription product that does not have the burdens of a high cost and immunosuppression of monoclonal antibodies.

5. Discussion

The historical progress in the management of HF has been presented. Highlighted is the complex pathophysiology of HF and consequently its multimodal therapeutic management. From the initial use of furosemide for fluid overload and digoxin for inotropic and chronotropic support, therapies are now directed against the maladaptive response of the RAAS, sympathetic, and natriuretic systems. With the consequent use of ACEI, aldosterone and neprelysin inhibitors, we can treat HF more effectively through nuanced combinations of the many therapeutic agents now available. Combination therapeutic regimens are now tailored to a patient's needs, therapeutic response, risk factors, and side effects [50]. More recently the efficacy of the SGLT2i medications to treat HF has been recognized. This includes management of the more complex HFpEF. Although SGLT2i were initially indicated to treat Type 2 diabetes, studies have revealed that they can treat HF in non-diabetic patients. This prompted the question of what is its MOA in treating HF? The answer has not been determined but there is evidence that it may be from the antioxidant activity of SGLT2i. Since HF is known to be negatively influenced by OS, providing an antioxidant should be beneficial. However, the SGLT2i have a diverse MOA. In order to definitively determine if antioxidants can counter OS, studies would best use a product with focused and significant antioxidant activity. GSH could be that product. Finally, evidence has been presented that a novel nano-product, the G-C complex, can therapeutically deliver GSH. This should prompt studies with its use. If therapy with GSH directed against OS is proven to be effective, antioxidants would be another "arrow" in the quiver of HF management.

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Abbreviations

The following abbreviations are used in this manuscript:

HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
MOA	Mechanism of action
SGLT-2i	sodium-glucose transport-2 inhibitors
ACEI	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker
RAAS	renin-angiotensin-aldosterone system
NP	natriuretic peptide
BMP	B-type natriuretic peptide
ARNI	angiotensin receptor-blocker/neprilysin inhibitor
GSH	glutathione

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NAC	N-acetyl cysteine
G-C	Glutathione-cyclodextrin

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