Abstract

Introduction
Diseases are in constant evolution, and new diseases spring into our world. The changes can be subtle and often overlooked. The article Alternative View of Congestive Heart Failure Exacerbations: Role of Lymphatic Function and Inflammation examines the lymphatic system. This article implies that heart failure exacerbations frequently occur due to an adverse perturbation of the periphery as opposed to the decline of central cardiac function.

Hypothesis
Heart failure occurs due to environmental factors that affect the periphery. A large number of patients have evolved into a larger species suffering from obstructed sleep apnoea, metabolic syndrome, recalcitrant hypertension and inflammation. A more common presentation of heart failure is the right heart failure.

Evaluation of hypothesis
Heart failure is not unique and the disease continues to evolve. Peripheral stressors include salt, systemic inflammation of diabetes and diet, obesity and obstructive sleep apnoea. These environmental factors stress the right heart causing oedema and fatigue. Left heart failure eventually ends in right heart dysfunction. These factors make right heart failure a significant problem that requires targeted therapy.

Conclusion
Potential therapies for right heart failure are presented directing future clinical trials. The lack of knowledge on heart failure medications has an effect on circulating stem cells, inflammation and lymphatic function, which makes the cardiologist crotchety. A crotchety cardiologist wants to understand the mediators of peripheral compensation.

Introduction
Life seems to slip faster as you age, perhaps explaining the crotchety disposition of old cardiologists. Advances in medicine fail are slow; this has an impact on improving the condition of many patients. The direction of therapeutics does not incorporate new paradigms; instead, it clings to old familiar dogma. Medical haemodynamic therapies seem to have come to a halt, favouring a mechanical approach to haemodynamics with the durable ventricular assist device (VAD). In addition, patients with right heart failure require a total mechanical heart.

Advances in heart failure therapy are not being pursued because old dogma gets in the way of new paradigms. The article Alternative View of Congestive Heart Failure Exacerbations: Role of Lymphatic Function and Inflammation examines the lymphatic system, which controls interstitial fluid homeostasis and inflammation. This article implies that heart failure exacerbations frequently occur due to an adverse perturbation of the periphery as opposed to the decline of central cardiac function. The symptoms and physical exam findings are the result of the failure of the lymphatic system to compensate for the failing heart. Inflammation is the task of the lymphatic system and is a cornerstone in all chronic disease. If we had chosen to conquer inflammation instead of the thrombus, we would be 50 years ahead of our current therapeutics.

Hypothesis
Heart failure occurs due to environmental factors that affect the periphery. A large number of patients have evolved into a larger species suffering from obstructed sleep apnoea, metabolic syndrome, recalcitrant hypertension and inflammation. A more common presentation of heart failure is the right heart failure.

The disease process of heart failure is evolving. Maybe it takes an old cardiologist to recognize the changes. Diseases are in constant evolution, and new diseases spring into our world. The changes can be subtle and often overlooked. Examples of obvious disease evolution include rheumatic fever and rheumatic heart disease that began to decline before the invention of penicillin. Smallpox has been completely eradicated. Childhood diseases have been modified by vaccines, and new diseases occur because of incomplete immunity. The AIDS epidemic is relatively new, which broke out in the twentieth century. An evolutionary disease caused by changing environmental factors, less sleep with more calorie ingestion, sedentary work styles, refined freely available carbohydrates and inflammation—is diabetes mellitus type 2.

Inflammation's role in causing central cardiac decline and its peripheral manifestations of loss of compensation should be aggressively addressed. Heart failure doctors need to begin to think about peripheral therapies and central therapies for heart failure. Central therapies have revolved around haemodynamics of cardiac function and generally have considered only one heart—the left heart—in those haemodynamic considerations. This article discusses the evolution of heart failure.

Evolution of heart failure: Crotchety old cardiologist

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Evaluation of hypothesis

The author has referenced some of its own studies in this hypothesis. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

Heart failure is not unique and is influenced by environmental factors and therapies. Acute pulmonary oedema from decompensated heart failure was easy to recognize and treat. Before the invention of diuretics, bleeding the patient would give respiratory relief. The dramatic preload reduction of bleeding would alleviate symptoms but would not cure the patient. We are still unsure whether preload reduction leads to better outcomes. Half a century ago, before hypertensive therapies and population weight gain, the presentation of heart failure was described as peripheral oedema with pulmonary vascular congestion in the textbooks, and the goal of therapy was to rapidly reduce the filling pressures. Those patients still exist today; however, their numbers are dwindling. The disease has evolved because more patients are being treated for hypertension and are already on heart failure medications. Our patients have evolved into a larger species suffering from obstructed sleep apnoea, metabolic syndrome, recalcitrant hypertension and inflammation.

Consequences of hypothesis

Our practice has evolved from treating one heart—the left heart—to treating both the right and left heart. Right heart failure and low output is becoming a more frequent presentation and cannot be managed as typical left heart failure. VADs are contraindicated. The right heart is sensitive to beta blockade. Restrictive disease requires increased heart rate since the ventricle is already too full and can be managed by emptying it more frequently. The interventricular septum can help both ventricles. In left bundle branch block (LBBB), the septum is paradoxical and responds well to biventricular pacing. Right heart failure can be improved with the induction of paradoxical septal motion, since the septum aids the right heart. This is the natural remodelling that occurs with pulmonary hypertension. Cascaded pacing alternating between the left and right ventricles should be pursued to rescue patients with right heart failure. Patients with right heart failure have symptoms of fatigue, abdominal pain, swelling, cough, dyspnea and inability to sleep. Their symptoms are more subtle than those of the left heart failure. All left heart failures either improve or evolve into right heart failures.

Hidden salt in fast foods and in almost all food preparations adds to volume overload. Diets can be inflammatory adding to systemic inflammation. A heart failure patient is particularly susceptible to this inflammation. This helps in explaining the clustering of heart failure admission after refined carbohydrate- and salt-rich holidays. New low-inflammatory diets in addition to low-sodium diets need to be developed. The extra stress on gut lymphatics by right heart failure adds to the inflammatory response, further degrading both peripheral and central function.

Discussion

Therapeutics needs innovation to meet the new challenges in heart failure. In addition, our therapies need to be selected based on their potential to remodel the heart. Anversa observed that there is no terminal differentiation in the heart and that stem cells could repopulate the heart. A new model of disease is presented. Health is defined when degeneration and regeneration processes are in balance with inflammation being the fulcrum between the two. Inflammation is both beneficial in repair and detrimental by promoting degeneration. We have not incorporated this concept into mainstream medicine. All our therapies need to be re-examined with regard to their potential to increase circulating stem cells and modify inflammation. These processes are innate to remodelling of cardiac anatomy. We may find that beta agonists may improve lymphatic function and/or peripheral function, but negatively remodels the heart preventing cardiac repair.

Therapies for the evolving right heart failure patients need to be advanced. My therapies consist of the following:

- Exercise to increase circulating stem cells—peripheral therapy
- Weight loss and continuous positive airway pressure (CPAP) to reduce inflammation and relieve airway obstruction of obesity—peripheral therapy
- Low-inflammatory, low-calorie, no simple carbohydrate diet, low-sodium diet—peripheral therapy
- Spironolactone to improve lymphatic function, decrease fibrosis and possibly reduce inflammation—peripheral and central therapy
- Ranolazine for diastolic function and arrhythmia (500 mg per day with renal insufficiency BID if no kidney compromise)—central therapy and peripheral therapy to be determined
- Sildenafil to improve right heart contractility and reduce pulmonary afterload—central therapy
- Right ventricular pacing transitioning to Bi-V—central therapy
- Lymphedema pump—peripheral therapy (trial needed)
- Erythropoietin for anaemia due to inflammation—peripheral therapy (controversial but Fick’s law states if the cardiac output is low then increased haemoglobin can compensate)
- Warfarin, ACEI, Plavix, for anti-inflammatory and anti-thrombotic—peripheral and central therapy

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• For decompensation requiring hospitalization, low-dose nesiritide 0.005 mcg/kg/min—low-dose peripheral therapy and high-dose central therapy (needs clinical trial on lower dosage administration, outpatient subcutaneous is very appealing)
• Reintroduce beta blockers when right heart failure has resolved—central therapy
• Digoxin 0.125—central and peripheral therapy (I am an old cardiologist and I know this old drug still works when dosed properly.)
• If nothing else is working, use beta agonists—which is a peripheral therapy but adverse to central therapy causing negative remodelling12 (Inotropic medications should only be used for short intervals.)
• Classification of heart failure therapies which attempts to classify therapies into central or peripheral therapies, regenerative or degenerative, and affect inflammation (Table 1).

Conclusion
These recommendations should not be construed as guideline recommendations. They describe the targets of therapy as central and peripheral, which is a new concept in heart failure management. The approach has to be moulded to the individual and as the individual changes, the approach has to be adjusted. I am crotchety because I want to know the effect of heart failure medication on circulating stem cells, inflammation and lymphatic function. These factors are powerful mediators of peripheral compensation.

Table 1  Classification of heart failure therapies

<table>
<thead>
<tr>
<th>Medication or Intervention</th>
<th>Central Mediated</th>
<th>Peripheral Mediated</th>
<th>Degenerative</th>
<th>Proliferative</th>
<th>Inflammation</th>
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<tr>
<td>Exercise</td>
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<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Lower</td>
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<td>?</td>
<td>?</td>
<td>Lower</td>
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<tr>
<td>Low CHO diet</td>
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<td>?</td>
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<td>?</td>
<td>Lower</td>
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<tr>
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<td>?</td>
<td>?</td>
<td>?</td>
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<td>Raise</td>
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<td>?</td>
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<td>?</td>
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<td>?</td>
<td>?</td>
<td>?</td>
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<td>?</td>
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<td>?Yes</td>
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</table>

Abbreviations list
LBBB, left bundle branch block; CPAP continuous positive airway pressure; VAD, ventricular assist device

References