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INFLAMMATION A POTENTIAL TARGET FOR THERAPEUTIC INTERVENTION IN HEART FAILURE

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Introduction

The concept of chronic heart failure (CHF) has evolved over time from just a simple "pump-failure" to a more complex syndrome involving the activation of different compensatory mechanisms. Activation of the immune system, for example, can result in the production and release of proinflammatory cytokines, production of antibodies, and activation of the complement system.

Several conditions contribute to the development of CHF. Initially, the heart is exposed to a primary insult such as myocardial infarction (MI), hypertension, viral infection or toxins (e.g., ethanol). The subsequent loss of myocardium, due to all compensatory mechanisms, creates a localized or generalized muscle dysfunction. Finally, the myocardium becomes more defective and weaker, producing symptoms typical of CHF.

The immune activation is part of the pathophysiology of heart failure. It can be divided into two broad categories: 1) immune activation secondary to cardiac injury, and 2) immune activation by direct antigenic stimulation. In the first category, new antigenic peptides are present in the myocardium and have the capacity to induce an immune response. Two common examples are the presence of numerous inflammatory cells at the area of infarction after an acute MI, and antibodies against myosin found in patients with idiopathic dilated cardiomyopathy (IDCM) (Figure 1). The second category is characterized by two clinical scenarios: acute cardiac allograft rejection and acute myocarditis. The myocardium of a heart transplant recipient undergoing rejection is infiltrated by mononuclear cells, B and T lymphocytes that are capable of producing cytokines and cardiac dysfunction. In patients with acute myocarditis, the cardiotrophic virus infects the cardiac cell and triggers multiple immune mechanisms involving mononuclear, T and B cells, in turn producing inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin (IL)-6 and releasing free radicals that affect cardiac function. Clinically, both conditions characteristically produce revers1ble myocardial dysfunction, and biopsy findings from both pathologies may be indistinguishable. Therefore, inflammation plays a significant contributory role in the pathogenesis of CHF.

Many studies have shown increased plasma levels of pro,nflammatory cytokines (i.e., TNF-a and IL-6) in patients with CHF. Normal myocardium does not contain TNF-a; however, as myocardial function starts failing, TNF-o: receptors of type I and II over-express in the myocardium.[1] In addition, increasing evidence suggests that both T and B cells are actively involved in CHF. Our group at the Methodist DeBakey Heart & Vascular Center studied the role of B-cell activation during acute exacerbations of heart failure 1n patients with CHF and found a three-fold increase in CD69 expression that returned to normal by six weeks, which may be related to a preferential activation of B cells but not T cells during acute heart failure decompensation.2

Chronic heart failure is clearly a complex syndrome, and immune activation plays an important role in the initiation and further perpetuation of myocardial dysfunction.

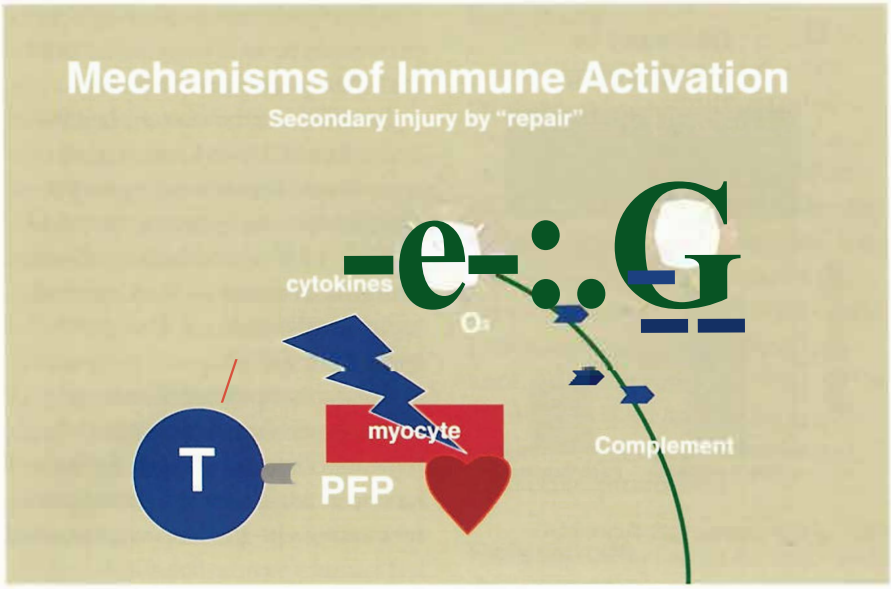

Figure 1. Pathway of immune activation in chronic heart failure (secondary injury). After a myocardial infarction or cardiac injury, new antigenic peptides are present in the myocardium and are able to induce an immune response. The initial immune response involves the development of T cell-specific and antibody responses and complement activation. B = B cells; M = macrophage/monocyte; PFP = pore-forming proteins; T = T cell.

Nonconventional Modalities to Treat Heart Failure

Immune adsorption (IA) and plasrnapheresis are two similar broad-spectrum immunomodulatory strategies used to tackle the variety of immune system components involved in the pathogenesis of heart failure, and both have demonstrated promising results.

Immune Adsorption

Disturbances in the cellular and hurnoral immune system have recently been linked to the pathophysiology of heart failure. Quite a few studies have identified several antibodies against various cardiac proteins in patients with heart failure, e.g., contractile proteins and I-receptor antibodies against mitochondrial proteins.[3] IA is a technique that has been used in Europe to remove specific antibodies from the circulation in heart failure patients. The procedure is founded on the utilization of ligands and adsorbers extracorporeally to remove serum irnmunoglobulins and immune complexes.

As we and others believe, cardiac antibodies are very important culprits in cardiac dysfunction, and their removal would improve cardiac function.[4, 5] Several small trials have evaluated the efficacy of eliminating cardiac autoantibodies through immune adsorption in stabilizing or slowing the progression of CHF. One of the first reports was a prospective, case-control study of 34 patients who had high anti-PI-adrenoceptor antibodies and were listed for heart transplantation. All of them underwent IA during five consecutive days. After the treatment, left ventricular ejection fraction (LVEF) increased from 22% to 38%, and there was no evidence of anti- 1-adrenoceptor antibodies in the serum at three-months follow up. These findings suggest that Pl antibodies play an important role in the pathogenesis of heart failure.[6]

Other small, nonrandomized studies on patients with dilated cardiornyopathy who underwent IA for five days evaluated either cardiac hemodynamics or LVEF, NYHA functional class, and myocardial inflammation. All demonstrated significant improvements in cardiac output and decreases in both mean arterial pressure and mean pulmonary arterial pressure. The treated groups had a significant decrease in I-receptor autoantibody levels, increase in LVEF, improvement of NYHA class, and decrease in inflammation on endomyocardia1 biopsy compared with the controls.[7, 8] More recently, repeated IA treatments at monthly intervals were compared to just one course of therapy, and LVEF improvement was found after six months.[3]

All of the trials mentioned have shown either significant improvement in LVEF and NYHA functional class or decreased inflammation, mainly in patients with dilated cardiomyopathy who had antibodies removed in the serum by IA. However, it is still unclear whether the benefits found in these patients were due to antibody removal alone or to a broader nonspecific immune modulation.

Plasmapheresis

Plasma exchange, or plasmapheresis, is a form of nonspecific immunomodulatory therapy that has proven efficacious in a variety of autoimmune conditions. During plasmapheresis treatment, venous blood is removed, and plasma is separated from the cells through either centrifugation or membrane filtration. The cells are then reinfused together with 5% albumin, crystalloid solution, or fresh frozen plasma. Some of the benefits of plasma exchange are the reduction of circulating autoantibodies, downregulation of B-cell responses, and

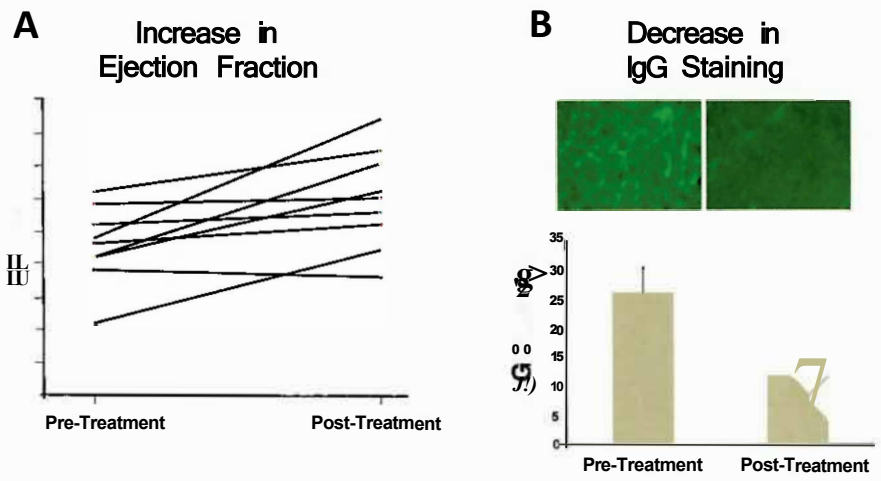

Figure 2. Changes in cardiac function and reduction of anti-cardiac IgG deposition in human failing myocardium following plasmapheresis. Figure 2A shows the changes in left ventricular ejection fraction in individual patients at baseline (prior to plasmapheresis) and at three-month follow-up. Figure 28 shows staining scores in the myocardial biopsies at baseline and at three-month follow-up after plasmapheresis.

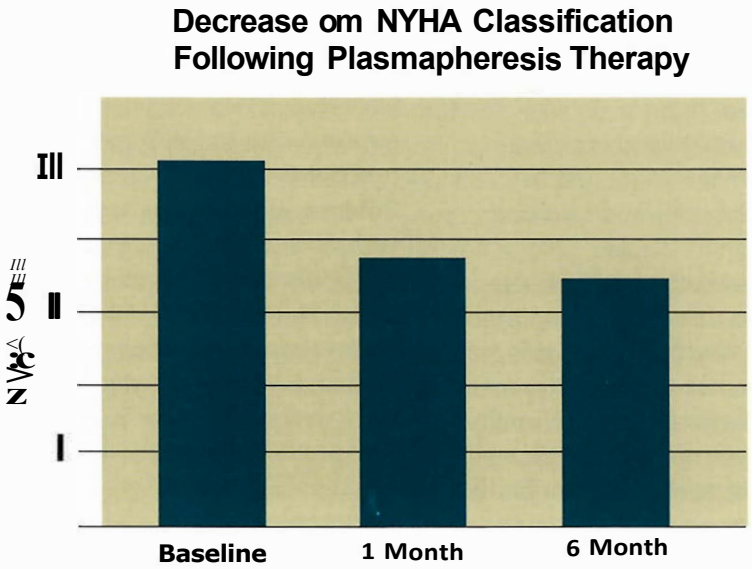

Figure 3. Changes in functional class following plasmapheresis. NYHA functional class scores were obtained from patients at baseline prior to beginning plasmapheresis and at 1 and 6 months following plasmapheresis treatment.

decreased cytokine production, all of which are potentially important in the progression of heart failure.

The molecules most successfully removed by plasma exchange are those that are mainly present in the intravascular space and have a long half-life, such as IgG, IgM, and low-density lipoproteins; however, those that are consistently distributed in the intravascular and extravascular space cannot be reliably and persistently removed. A reduction of intravascular IgG of up to 70%-85% has proven possible when combined with immunosuppression.9 On the other hand, since the majority of IgM is present intravascularly, the removal of IgM by plasmapheresis is more efficacious and the result more persistent.

Evidence of the use of plasmapheresis in CHF is limited. Case reports and series have reported plasmapheresis to be successful in treating CHF in the setting of autoimmune diseases such as systemic lupus erythematosus, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, polymyositis, or a viral infection. [9,10] In other contexts, plasmapheresis has been used in heart transplant recipients who develop unexplained left ventricular dysfunction. In different case series,[10-11] patients who presented with rejection that was resistant to conventional immunosuppressive treatment and who subsequently underwent plasmapheresis had an improvement in CHF symptoms and regression in vascular inflammation, which was evidenced by decreases in endothelial swelling, interstitial edema, and lymphocytic infiltrates.

In our own unpublished experience, 10 heart transplant recipients underwent plasmapheresis for depressed LVEF < 20% but with normal coronary angiography and no evidence of cellular rejection on endomyocardial biopsies. The majority of the patients (90%) showed a significant increase in ejection fraction with plasmapheresis (LVEF increase mean of 26.3%). This observation is important to validate the potential role of plasma exchange as a therapeutic strategy in patients with immune-mediated cardiac dysfunction.

Even though activation of the humeral and cellular immune response during acute and chronic CHF is well documented, plasmapheresis as a coadjutant treatment in nontransplant CHF patients with LV dysfunction has not been studied widely. We recently finished

a nonrandomized small clinical trial of plasmapheresis in patients with advanced cardiomyopathy, LVEF less than 30%, and NYHA functional class II- IV Our treatment protocol consisted of five courses of plasmapheresis every other day, over a three-hour period, utilizing albumin reconstitution following each treatment and intravenous gamma globulin at 500 mg/kg after the fifth course of treatment. Baseline measurements of hemodynamics, echocardiography, plasma samples, and right ventricular endomyocardial biopsies were obtained. We found that plasmapheresis significantly i$_{mp}$roved LVEF, Quality of Life (QoL), and NYHA functional class in the majority of patients (seven out of nine) included in this study (Figure 2 and 3). In addition, we found that failing human hearts had an IgG deposition in the myocardium that can be significantly reduced by plasmapheresis. The decrease in antibody deposition correlated with the i$_{mp}$rovement in cardiac function (Figure 2B). These data collectively suggest a role of humeral immunity in the progression of heart failure.

These results confirm previous studies that found FcyR, a receptor for the constant region of immunoglobulin, able to activate cardiac cells, which in turn may lead to apoptotic cell death.[12,13] They also highlight our own myocardial biopsy findings, which showed a high frequency of antibody deposition in various stages of failing human myocardium.

Summary

In conclusion, plasmapheresis produces effects similar to other immunomodulatory therapies and can safely be applied to symptomatic heart failure patients. However, plasmapheresis in combination with intravenous immunoglobulin produces a synergistic effect that could increase cardiac antibodies clearance, allowing faster recovery of the immune system and down regulation of cytokine expression and antibodies production.

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