

"Renal Failure and Need for Heart Replacement: a Conceptual Framework". (Revisiting Concepts of Patient for Chronic Mechanical Assist Support)

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Riassunto

La terapia di assistenza meccanica del ventricolo sx (LVAD) è, al giorno d'oggi, nel medesimo stato del trapianto di cuore 30 circa anni orsono, quando questa chirurgia veniva vista come una terapia sperimentale da riservare ad un piccolo numero di pazienti. Questa situazione di fatto scaturisce dalla perdita di evidenza scientifica che la LAVD sia efficace nel prolungare la sopravvivenza dei pazienti con scompenso cardiaco (SC) avanzato in virtù dei risultati insoddisfacenti degli studi sino ad oggi condotti. Per cercare di superare questa importante problematica, con il presente lavoro si propone un approccio clinico nuovo che cerchi di coniugare la selezione adeguata del paziente da indirizzare alla terapia di assistenza ventricolare meccanica e il cruciale "timing" dello impianto stesso. Poiché la funzione renale in corso di SC è il più chiaro indicatore di funzione cardiaca la indicazione nuova è la applicazione della LAVD in quei pazienti che mostrano ritenzione di liquidi a dispetto di un trattamento farmacologico ottimale.

In conclusione, oggi forse è arrivato il momento di pensare alla LAVD non come una terapia di "salvataggio" per pazienti con SC in fase terminale ma come possibilità terapeutica da destinare a quei pazienti che hanno poco o nulla da guadagnare nonostante la terapia farmacologia ottimale e che presentino caratteristiche di rischio di imminente disfunzione multi-organo, condizione determinata sostanzialmente dal peggioramento della funzione renale.

Abstract

Left Ventricle Assist Device (LVAD) therapy is currently at the same stage of development as orthotopic heart transplantation was about 30 years ago, when it was regarded as mere experimental surgery for a small number of patients. This situation is mainly due to lack of scientific proof that LVAD therapy is effective in prolonging survival in very severe heart failure patients. This approach mainly derives from the poor results of LVAD therapy in severe heart failure patients. To overcome this problem of the lack of scientific evidence, we propose a new clinical approach to simultaneously identify both the most suitable patient cohort as well as the best time for LVAD implant. Since kidney failure is the clearest indicator of progressive heart failure, we propose applying LVAD therapy in the patients who have progressive fluid retention despite optimal medical therapy. In conclusion, the time has perhaps now arrived to shift from the use of LVAD therapy as rescue strategy for terminally ill patients to a therapy for patients who have nothing more to gain from ongoing medical therapy and who clearly risk imminent multiple organ failure, heralded by progressive kidney insufficiency.

Key words

Advanced heart failure, kidney, LVAD, heart replacement, heart transplantation

Introduction

Currently cardiologists and internal medicine specialists treat the bulk of hospitalized heart failure (HF) patients and only refer the most difficult cases to specialized heart replacement centres¹. These difficult cases include those eligible for heart transplant (HTx) based on age (usually under 65), with signs and symptoms of HF due to pump failure and/or those refractory to optimal medical therapy. Older patients and/or patients with co-morbid conditions, contraindications to immunosuppressive therapy or end-stage heart failure are currently not considered for HTx or any other alternative therapy. This situation persists despite evidence to support the use of implantable left ventricle assist devices (LVAD) in improving successful transplantation rate for unstable patients on waiting lists for HTx²⁻³. In fact, LVAD therapy is only currently used as an emergency rescue strategy for terminally ill patients. Moreover, LVAD therapy is currently at the same stage of development as orthotopic HTx was some 30 years ago. Orthotopic HTx was then regarded by cardiologists as just

a costly and dramatic surgical rescue therapy appropriate for very few terminal patients waiting for a donor heart.

The result is that HF patients needing heart replacement, ineligible for HTx mostly because of advanced age, but eligible for LAVD therapy mostly find themselves abandoned, with no effective therapy on offer.

This article offers a new conceptual framework for the use of LVAD therapy for patients ineligible for HTx or with a poor prognosis despite eligibility.

Background To The Clinical-Pathophysiology Assessment

Ventricular impairment takes place after myocardial injury leading to heart failure (HF), the clinical condition in which blood supply to organs and tissues is impaired by progressive cardiac dysfunction and kidney is the organ immediately affected by decreased blood perfusion. In this circumstance ATII preserves urine output through increased glomerular filtration fraction¹³ by causing constriction of the efferent arteriola. Initially, natriuretic polypeptide

(ANP, BNP, etc) production rapidly increases enhancing natriuresis, and vasodilatation. Unfortunately their effects are suppressed by the development of exceedingly high levels of neutral endopeptidases, which rapidly degrade these helpful molecules¹⁵⁻¹⁶. The progressive drop of cardiac output enhances ATII effect on afterload increase, worsening cardiac performance and affecting, in turn, kidney perfusion and urine production that is maintained through the increasing filtration fraction and consequently fluid retention and splanchnic congestion therefore become the most prominent features of the heart failure picture and need to be treated with diuretics and Angiotensin Converting Enzyme - Inhibitors (ACE I)¹⁷. The kidney reacts to the impaired haemodynamic condition with the constriction of the efferent arteriola due to production and secretion of angiotensin II (ATII). The consequence of these modifications is reduced urine output through increased glomerular filtration fraction⁴⁻⁷. This causes fluid retention and splanchnic congestion which become the most prominent features of the heart failure syndrome and need to be treated with diuretics and ACE Inhibitors (ACE I)⁸.

Clinical Implications

In severe HF patients the need for increasing diuretic dosage to control signs and symptoms of splanchnic congestion causes hypotension. This adds to the hypotensive effects of ACE-I and causes ACE-I intolerance. ACE-I intolerance is a potent negative prognostic indicator, as

documented in the analysis of several subgroups of patients in prominent randomised prospective studies⁹. As shown in the CONSENSUS population, there is a close exponential relationship between mean arterial pressure (78 mmHg) and progressive renal dysfunction¹⁰⁻¹¹. ACE I intolerance due to low systolic blood pressure, associated with worsening symptoms, is coupled to pre-renal kidney insufficiency and further compromises kidney function which worsens patient prognosis (Fig. 1). The same evidence comes from studies focusing on the effect of beta blockers in advanced heart failure populations. In NYHA Class IV patients, the scenario is of beta blocker intolerance, low systolic blood pressure (below 100 mmHg), and reduced mean arterial pressure (≤ 75 mmHg), associated with a low sodium concentration (< 137 mEq/L)¹². It is clear that patients with severe cardiac insufficiency, who are intolerant to beta blockade, are at greater risk. However, tolerance levels seem to match, in the short and medium term prognosis, those patients with a less advanced condition. This observation is consistent with the fact that in HF patients who

tolerate beta blockers, (despite severe pre-renal azotemia), the improved possibility of survival offered by this drug is equal to the benefit in patients with preserved renal function¹²⁻¹³. Data taken from studies in patients affected by very advanced cardiac insufficiency show that a systolic pressure equal to or less than 105 mm Hg, frequently results in neuro hormonal pharmacological intolerance with the appearance of drug-related symptoms¹⁵. Among these, the worsening of renal insufficiency is an immediate unfavourable sign depicting a more severe haemodynamic disorder that affects all vital organ functions heralding a bleak short-term prognosis. Thus, the best indicator of negative short term outcome in HF patients is moderate renal impairment (creatinine $> 1,5$ mg/dL or GFR < 44 ml/min) rather than NYHA functional class and/or left ventricle ejection fraction alone¹⁶⁻¹⁷. In addition, persistence of low blood perfusion and splanchnic congestion affects the entire body, leading to diffuse hypoxic damage to tissues and stimulating an inflammatory response via increased production of

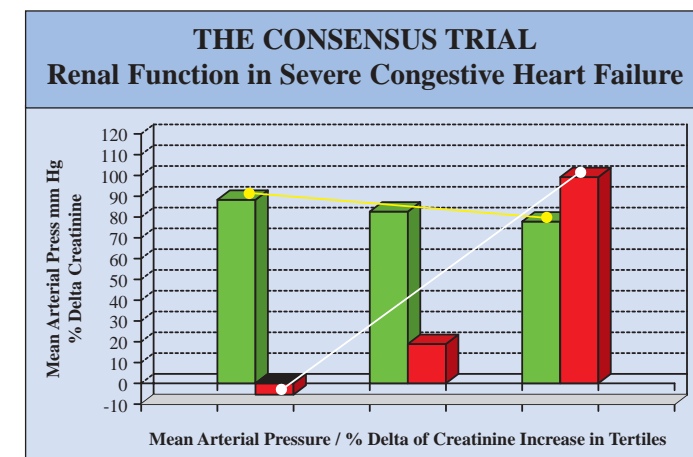


Fig. 1 - Histograms compare CONSENSUS trial population divided by tertiles based on mean arterial blood pressure value, depicting variation of creatinine serum concentration in the 3 patient groups (See text for comment).

cytokines (TNF alpha, IL6) with further deterioration of end organ function: namely heart, kidney and micro-circulation¹⁸⁻²¹. The obvious aim of therapy dealing with low systolic blood pressure and progressive renal impairment is to improve myocardial performance and organ perfusion. In this clinical scenario, parenteral inotropic support is mandatory. Inotropic drugs improve end organ function and reverse end organ damage in direct proportion to the increase of cardiac output

achieved. Inotropic support may be used as a short term bridge to HTx in patients refractory to other anti-failure treatment. However, this strategy is only useful in the short term. Moreover, prolonged inotropic support, usually required by severely sick patients, is associated with a reduced survival²²⁻²⁴. If inotropes are to be successfully used as a bridge or as a rescue therapy, then it is crucial to establish appropriate criteria for inotropic induction and for subsequent weaning of the patient from the treatment²⁵.

Criteria for the introduction of inotropic therapy

The persistence of a low cardiac output syndrome with high filling pressure, visceral congestion and with the reduction of urine output despite therapy with ACE-I and beta blockade is an unfavourable condition where it is often necessary to reduce if not indeed suspend ACE-I and beta blockers. If, despite the suspension of drug treatment, the clinical picture does not improve or renal damage

increases, medical therapy with inotropic support becomes inevitable²⁶. The objective of inotropic therapy is to achieve sufficient organ function to allow stability of the urine output and relative patient well-being. The next objective is to wean the patient from inotropic drugs while retaining hemodynamic stability.

The indicator of organ perfusion most readily available is the arterial pressure. However, in the presence of a severe cardiac output reduction the proportional pulse pressure [(systolic pressure-diastolic pressure/ systolic pressure)] can be 25% of normal²⁷. Hence, haemodynamic monitoring with a Swan-Ganz catheter is important because it allows optimal titration of drug²⁸⁻²⁹. It is worth underlining that in patients with advanced cardiovascular insufficiency, ACE I have not shown a significant benefit compared to the therapeutic action of pure vasodilators such as hydralazine or nitrates³⁰.

Consequently, therapeutic goals should be aimed at preserving and maintaining long term efficiency of organ perfusion. If we consider the importance of weaning as a specific clinical objective to be reached and maintained, it is essential to have all the necessary information to hand,

even at the cost of prolonging patient hospitalisation. In this phase, the presence of low arterial pressure incompatible with acceptable patient autonomy, and increasing renal insufficiency, indicate inotropic dependence. In patients with these characteristics, the prognosis for successful pharmacological treatment alone, is particularly poor. In this situation a HTx would seem the best current remedy. However, an alternative therapeutic strategy has recently been proposed and subjected to a prospective randomised study.

The REMATCH trial³¹ enrolled an extremely advanced HF population, never studied before in controlled HF studies. REMATCH investigated the long term use of LVAD in patients with end stage HF. The severity of HF in this population is illustrated by a comparison of systolic

blood pressure and creatinine levels of patients enrolled in the CONSENSUS¹⁰ and in the COPERNICUS trial³² with the REMATCH³¹ patient population. As shown in Fig. 2, levels of systolic blood pressure and plasma creatinine were similar in the CONSENSUS and COPERNICUS

groups, while they were consistently worse in the REMATCH patients, where 71% received parental inotropes at the time of randomisation. Moreover, REMATCH patients on inotropic support had statistically significant lower systolic blood pressures, lower serum sodium concentrations and higher pulmonary capillary wedge pressures (Fig. 3).

These data are consistent with expected survival rate of outpatients on home inotropic infusion, which is less than 50% at 3-6 months³³⁻³⁴.

The REMATCH LVAD group demonstrated the greatest survival rate of all of the above studies which accounts for the superiority of the surgical therapy reported by Stevenson¹⁶. It is important to note that sudden death in the REMATCH population occurred rarely, accounting for only 5% of mortality in the control arm. This data reinforces the concept that the therapy of choice should target improved cardiac function rather than prophylaxis for dysrhythmias. The LVAD arm of REMATCH demonstrated a much higher percentage of survival rate than any other therapeutic option in all HF trials to date. This was true even though the LVAD group experienced a much higher adverse event rate, mainly related to infections (sepsis 41%) and mechanical failure. These adverse events, together with cerebrovascular accidents, were substantial causes of death (68%). Assuming that the incidence of these fatal causes can be halved,

and there is evidence that this is possible³⁵, this would have a significant impact on one and two year survival in the device group. A limited and achievable reduction in LVAD patient complications would therefore lead to this therapy becoming a real breakthrough.

AHF Populations - Comparison by creatinine level and systolic blood pressure

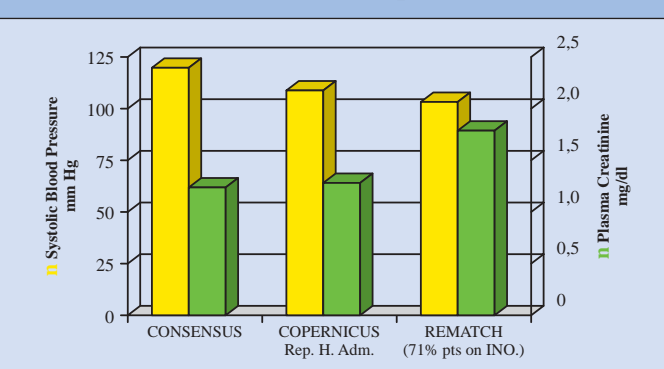


Fig. 2 - Average systolic blood pressure, pulmonary capillary wedge pressure, serum sodium concentration in the REMATCH patient cohort are compared between patients enrolled while were maintained only with oral drugs and the patient group that needed intravenous inotropes (See text for comments).

Two REMATCH Populations

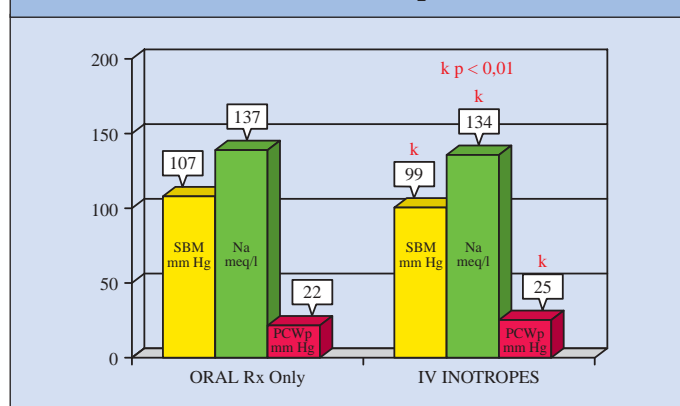


Fig. 3 - Mean systolic blood pressure, mean serum creatinine concentration in the 3 major advanced heart failure trials are compared in the figure. REMATCH study patient cohort presents lower systolic pressure and higher creatinine concentration (See text for comment).

A New Clinical Approach

Based on the data illustrated above, we can make some deductions. End stage HF patients requiring a heart transplant have limited survival prospect. Once patients are inotrope dependent this prospect becomes extremely limited and ongoing therapy results in high costs and poor quality of life. Until now, LVADs have been implanted in terminal patients as a rescue bridge therapy to heart transplant. However, a number of recent studies attests to the importance of intervention prior to the patient becoming terminal thus avoiding, or at least limiting, severe and/or irreversible kidney and liver dysfunction. This approach could positively influence the LVAD outcomes³⁵, primarily because of shorter and more efficient hospitalization and consequently with an early return to a near normal lifestyle on LVAD support. We are conscious that LVAD implantation is an expensive therapy. However, we think that the value of this therapy can be summarised as follows:

a) It decreases the risk of unsuccessful patient outcomes both during waiting time and at the time of heart transplant.

b) It decreases global medical costs during the final stages of HF.

c) It provides the patient with an acceptable quality of life while either waiting for a heart transplant or for improved myocardial performance. Experience gained from heart transplants is consistent with the above-listed prospectives²⁻³. Recently published data has outlined the superiority of LVAD therapy as a bridge to transplant, both with respect to overall survival from the waiting list, but also for a better post-transplant survival in the mid term follow up (up to 12 months) compared with HF patients chronically supported by intravenous inotropes (Fig. 4). This figure highlights the possibility of optimising donor use through a safer management of listed LVAD patients as Status 2 candidates, compared to unstable inotrope-dependent Status 1-1A candidates³⁶⁻³⁷.

It is noteworthy that 50% to 70% of LVAD patients waiting for a transplant are currently discharged from hospital, living near-normal lives in the community and with a relevant cost saving benefit to the healthcare system³⁸.

Profiling The Chronic Support Patient

The arguments outlined above illustrate that, up to now, LVAD therapy has almost exclusively been used for patients with an extremely poor prognosis (REMATCH³¹). However, now that the benefit of LVAD therapy has been

demonstrated, it is time to identify a patient population who could benefit most from this therapy. Indeed, we believe that it is now time to extend the benefit of LVAD therapy to a wider patient population. Hence, the application of LVAD therapy must shift from being purely a rescue strategy, carried out in mortally ill patients, to a semi-elective intervention for patients who have nothing more to gain from ongoing medical therapy and who have clear signs of progressive end organ dysfunction. Given the above arguments, we suggest that inotrope therapy should be implemented when symptoms such as reduction in urine output and low, symptomatic systemic blood pressure become apparent. When parenteral inotropic support does not produce an adequate and stable hemodynamic response leading to successful weaning, without prejudicing organ function, replacement therapy should be advised. The kidney seems to be the most reliable and sensitive indicator of adequate systemic arterial perfusion, in advanced heart failure. Declining glomerular filtration rate along with symptomatic hypotension and persistent

need for inotropic therapy despite appropriate weaning attempts, depict the condition of inotrope dependence²⁴⁻³⁹.

This seems to be the most reliable criteria for elective LVAD implantation, avoiding the inevitable progression to multiorgan dysfunction and failure. Indeed LVAD implantation in the face, of multiorgan failure is associated with a much poorer outcome⁴⁰⁻⁴².

LVAD improves utilization of doner hearts

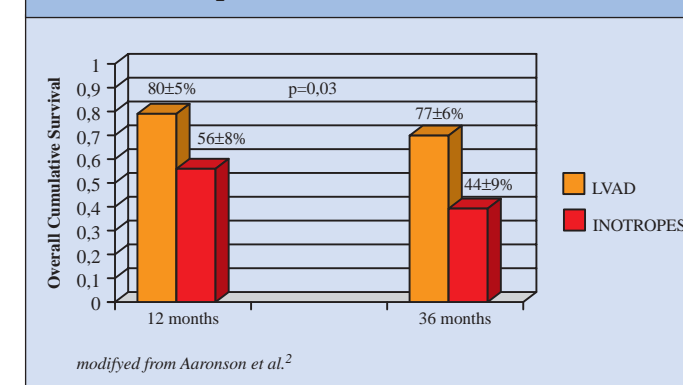


Fig. 4 - Overall survival for the LVAD and inotrope groups is depicted in the figure at 12 and 36 months from the onset of bridging support. From Aaronson et colF (See text for comment).

Conclusions

Recent experience has demonstrated that LVAD therapy can provide reasonable alternative for end stage HF patients for whom no other solution is available. These results have been obtained in an unusually old and sick population compared to the patients referred to HTx, mainly because of inotrope dependence. Based on these observations, it becomes important to focus on getting the message across to two major physician groups; cardiologists and specialized heart failure centres. Cardiologists should review their own decision-making process regarding selection and timing for device therapy, while specialized centres need to optimize LVAD patient management in order to minimize the incidence of adverse events. To optimize patient management a consensus decision should be reached in order to establish a more uniform patient selection process in a non-emergency setting. Because of the complicated nature of LVAD technology and the extremely high risk nature of the target population, large scale trials are both difficult to perform and involve questionable



ethics. The adoption of properly designed registries enrolling both patients on inotropic support and those on LVAD therapy, will allow for a more accurate analysis of patient management and outcomes. Registry data will also generate timely and more structured hypotheses to be tested in smaller and more feasible controlled trials.

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