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Summaries of featured articles

1- Stempien-Otero, MD; Deri Helterline, MS; Tabitha Plummer; Stephen Farris, MD; Andrew Prouse, MD; Nayak Polissar, PhD; Derek Stanford, PhD; Nahush A. Mokadam, MD. **Mechanisms of Bone Marrow-Derived Cell Therapy in Ischemic Cardiomyopathy With Left Ventricular Assist Device Bridge to Transplant.** *J Am Coll Cardiol.* 2015;65(14):1424-1434.

See also the Editorial comment:

Timothy D. Henry, MD, Heidi J. Reich, MD, Andreas M. Zeiher, MD

Of Mice and Men - The Best Laid Scheme? *J Am Coll Cardiol.* 2015;65(14):1435-1437.

The authors studied the evidence of engraftment and/or of vascular proliferation in prespecified areas of the Left Ventricle where bone-marrow derived stem cells had been injected at the time of LVAD implantation. Sham operation (injection of saline solution) was applied to the control group. The scope of the study was to evaluate the potential for applying combined regenerative therapy (stem cells) and unloading therapy (LVAD) to improve myocardial structure (and, consequently, function) in Pts with advanced heart failure due to ischemic heart disease.

Six Pts completed the study protocol (cell therapy arm), and their hearts were removed at the time of Heart Transplantation (HTX), which occurred at a highly variable distance from LVAD implant (47->400 days).

In contrast with other experimental and pioneer clinical studies, which in a reasonable proportion demonstrated an increase in microvascularization, contractility, and/or clinical status, this study did not obtain any evidence supporting the hypothesis that the injection of bone-marrow derived stem cells in partially scarred myocardium supported by LVAD could differentiate into new vascularisation or myocardial fibres, so limiting fibrosis and improving myocardial performance.

No complications were seen.

These results may derive from many reasons, as pointed out by the researchers and, with more details and criticism, by the authors of the editorial comment that follows the paper:

- end-stage disease with too extensive scarring, precluding the possibility of stem cells to exert paracrine activity and stimulate endogenous vital cells;
- unfavourable milieu for myocardial regeneration, due to (relatively) advanced age and high prevalence of diabetes in study population - although they resemble average advanced heart failure Pts undergoing LVAD implant as per current practices;
- low quantity and/or low differentiation potency of the injected cells;
- low standardisation of the entire protocol, as indicated for example by the wide variability of time interval between treatment administration and transplantation.

Neither the researchers nor the editorialists analyse the possible specific influence of mechanical unloading on the mechanisms of cell differentiation, angiogenesis, myocardial regeneration, fibrosis, and, ultimately, LV remodelling and reverse remodelling. In fact, it seems that LVAD followed by HTX has been utilised purely as a human experimental model, allowing to look directly at structural changes that occur (or do not occur) after bone-marrow derived endogenous stem cells injection. The readers can agree that "absence of evidence is not evidence of absence", as stated at the end of the editorial comment, and may still hope in the potential therapeutic efficacy of cell therapy for cardiac disease. However, they should also admit (and accept) that the objective of combining cell therapy and mechanical unloading to obtain clinically relevant structural tissue changes and myocardial recovery appears to be at a great distance from evidence-based application in the real-life setting of advanced/refractory heart failure due to ischemic heart disease.

2- Michael S. Kiernan, Amy L. French, David Denofrio, Yuvrajsinh J. Parmar, Duc Tinh Pham, Navin K. Kapur, Natesa G. Pandian, and Ayan R. Patel. **Preoperative Three-Dimensional Echocardiography to Assess Risk of Right Ventricular Failure After Left Ventricular Assist Device Surgery.** *Journal of Cardiac Failure.* Mar-Apr 2015; 21 (3): 189-197

Right Ventricular Failure (RVF) after LVAD implantation is a frequent complication, associated with increased mortality, morbidity, and length of stay. Thus, prediction of the risk of RVF is relevant for patient selection and for perioperative strategy planning. Different parameters and multiparametric scores have been demonstrated to be associated with RVF after LVAD implant, but no "gold standard" models have been identified so far, due to multiple reasons:

- different modalities to define RVF
- different sets of analysed variables, with focus on clinical and/or hemodynamic and/or echocardiographic parameters
- evolving LVAD technology
- evolving practices in patient selection and management.

The paper integrates preoperative 3-Dimensional echocardiographic measures (RVEDD, RVESV, RVEF) with multiple other parameters (clinical, biochemical, hemodynamic, and mono- and 2D-echocardiographic variables) for prediction of RVF, defined by the need for RV assist device and/or prolonged inotropic support > 14 days, in a cohort of 26 Pts undergoing continuous flow LVAD implant between 2008 and 2011. It is of note that 75% of the pts were classified as INTERMACS 1 profile, 46% experienced RVF, and baseline INTERMACS profile type 1 was the only clinical parameter statistically different in Pts who experienced or not post - op RVF. Among hemodynamic

and echocardiographic parameters, it is interesting to see that two very simple variables related to RV function in relationship with LV (i.e. RV/LV EDD Ratio, RAP/PCWP Ratio) predicted the occurrence of RVF. Other variables associated with different rates of occurrence of RVF were cardiac index (lower) and right ventricular stroke work index (lower). All 3-D acquired variables were significantly different between Pts with vs. without RVF, and 3-d Echo increased the accuracy of multivariate predictive model (best ROC curve with 90% sensitivity and 75% specificity).

Echocardiographic technique is described in details, while the impact of RVF on clinically relevant end points in this specific Pts cohort is not reported. The prevalence of INTERMACS 1 Pts is higher than generally observed in contemporary series, and may justify 1) the high rate of occurrence of RVF and 2) the relatively high value of cardiac index in no RVF Pts (2,4 l/min/BSA square meters), probably reflecting some efficacy of inotropic treatment preceding LVAD implantation. Being derived from retrospective analysis of available pt data, the feasibility of 3D echocardiography in Pts under evaluation for LVAD cannot be determined. However, as pointed out by the authors, despite its apparent complexity, 3d Echo measures may be superior than more commonly used 2-D Echo, due to the peculiar geometry of the right ventricle, both normal and pathological. Reproduction of similar results in terms of predictive accuracy in other Pts cohorts, with a different composition regarding INTERMACS profiles and a lower proportion of inotropic use, would reinforce the usefulness of this Echocardiographic tool.

3- Zachary C. Landis, Behzad Soleimani, Edward R. Stephenson, Aly El-Banayosy, and Walter E. Pae. **Severity of End-Organ Damage as a Predictor of Outcomes After Implantation of Left Ventricular Assist Device.** ASAIO J. Mar-Apr 2015; 61(2): 127-132.

The use of left ventricular assist devices (LVAD) is increasing in the management of patients with end-stage heart failure, either as a bridge to transplantation (BTT) or as destination therapy (DT). The optimal timing of implantation remains controversial. Sequential organ failure assessment (SOFA) score is used in critical care to quantify the severity of end-organ dysfunction, taking into account cardiovascular, respiratory, hepatic, renal, coagulation, and neurologic function. The authors examine the relationship between preoperative SOFA score and postoperative outcomes (mortality, length of stay and readmission rates) in LVAD recipients, and also evaluate the usefulness of this score for patient selection for LVAD implantation. Data from 97 patients receiving Thoratec HeartMate II (n=80) or HeartWare HVAD (n=17) device from January 2007 to April 2012, were studied. Baseline SOFA score was higher in DT pts (n=42) than in BTT pts (n=55), and in those with lower INTERMACS profile. Patients were divided into different subgroups according to the SOFA score (0-2: n=22, 3-5: n=46, 6-8, n=20; ≥ 9 , n=9).

In contrast with previous studies, there was no statistically significant difference in 30 days mortality between subgroups defined on the basis of SOFA score (zero for SOFA scores 0-2, n=22; and 13%, 10%, 11.1% for scores 3-5 [n=46], 6-8 [n=20], and ≥ 9 [n=9] respectively). On the other side, pre-implant SOFA score predicted long-term survival. The overall 1 year survival after LVAD implantation is 73.3%, and was 94.4%, 75%, 64.3%, and 28.6% for SOFA scores 0-2, 3-5, 6-8, and ≥ 9 respectively (p=0.001). SOFA score was significantly lower in survivors versus non-survivors at 6 and 9 months, and 1, 2, and 3 years after operation. The discriminatory value of SOFA score in predicting one-year mortality was shown both in DT and in BTT strategy, but with different threshold associated with very high or very low probability of survival.

The entire study cohort is made of less than 100 pts, thus the reliability of the observed SOFA score thresholds for prospective prognostic evaluation and decision making in individual patients is uncertain. The low/neutral impact of SOFA score on 30-day mortality may reflect improved early postoperative management with respect to previously published studies, but may also be the consequence of improved overall pt selection: multisystem organ failure may have different prognostic relevance according to duration, etiology (pure consequence of heart failure, or due to intrinsic extracardiac disease), and other variables such as pt age. However, its persisting influence on mid- to long-term outcome suggests that earlier LVAD implant could be considered in Pts with initial end-organ dysfunction, and also that Pts with advanced heart failure with significant extracardiac disease may have a limited benefit from LVAD therapy.

ASAIO Journal:

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Michael S. Kiernan, Amy L. French, David Denofrio, Yuvrajsinh J. Parmar, Duc Thinh Pham, Navin K. Kapur, Natesa G. Pandian, and Ayan R. Patel. Preoperative Three-Dimensional Echocardiography to Assess Risk of Right Ventricular Failure After Left Ventricular Assist Device Surgery. *Journal of Cardiac Failure.* Mar-Apr 2015; 21 (3): 189-197

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Editorial comment:

Timothy D. Henry, MD, Heidi J. Reich, MD, Andreas M. Zeiher, MD

Of Mice and Men - The Best Laid Scheme? *J Am Coll Cardiol.* 2015;65(14):1435-1437.

JOURNALS:

ASAIO JOURNAL, Mar-Apr 2015

JOURNAL OF CARDIAC FAILURE, Mar-Apr 2015

CIRCULATION HEART FAILURE, Mar 2015 and April 2015

EUROPEAN JOURNAL OF HEART FAILURE, Mar 2015 and April 2015

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