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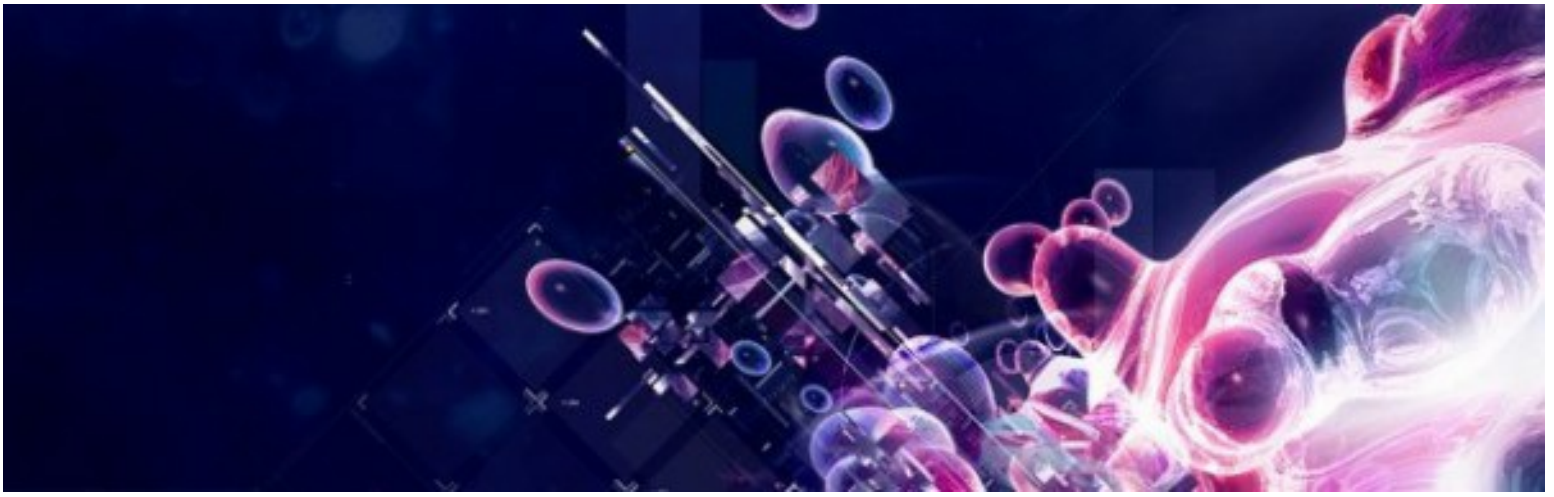

The Cost to Value Conundrum in Cardiovascular Healthcare Provision

Posted in Accountable Care Organizations, Affordable Care Act, Anemia, Atherogenic Processes & Pathology, Best evidence, Bio Instrumentation in Experimental Life Sciences Research, Biomarkers & Medical Diagnostics, Biomedical Measurement Science, Ca2+ triggered activation, Ca2+ triggered activation, Calcium Signaling, Cardiac & Vascular Repair Tools Subsegment, Cardiac and Cardiovascular Surgical Procedures, Cardiac muscle regeneration, Cardiomyopathy, Cardiovascular Pharmacogenomics, Coagulation Therapy and Internal Bleeding, Computational Biology/Systems and Bioinformatics, Curation, Curation methodology, Cytoskeleton, Diabetes Mellitus, Electrophysiology, Evidence-based decision-making, Experimental validation, Federal Budget Appropriations, Frontiers in Cardiology and Cardiovascular Disorders, Health Economics and Outcomes Research, Health Law & Patient Safety, Healthcare costs and reimbursement, Healthcare Reform, Historical relevance, HTN, HTN in Youth, Indigent Nutrition, Interviews with Scientific Leaders, Ionic Transporters Na+, K, Medical Devices R&D and Inventions, Medical Imaging Technology, Image Processing/Computing, MRI, CT, Nuclear Medicine, Ultra Sound, Medicare and Medicaid, Na-K transport, Na-K-ATPase, Nephrology, Nitric Oxide in Health and Disease, Nutrition, Nutritional Supplements: Atherogenesis, lipid metabolism, Origins of Cardiovascular Disease, Pharmaceutical Analytics, Pharmacogenomics, Pharmacologic toxicities, Pharmacotherapy of Cardiovascular Disease, Population Health Management, Genetics & Pharmaceutical, Population Health Management, Nutrition and Phytochemistry, Prescription Drugs Costs, Regenerative Biology and Medicine, Resident-cell-based, Skilled Nursing Facilities, Stem Cells for Regenerative Medicine, Stents & Tools, Synaptic vesicle, Systematic Error (Bias), Systemic Inflammatory Response Related Disorders, Technology Advance Assessment of, Technology Capital Expenses, Technology Transfer: Biotech and Pharmaceutical, Translational Effectiveness, Translational Science, Uninsured and Underinsured, Valves & Tools, tagged acute myocardial infarct, American College of Cardiology ACC, Antiarrhythmic drugs, arrythmias, Artificial Biosensor, Artificial cardiac pacemaker, Artificial heart, Bare-metal stent, Cardiac & Vascular Repair, cardiac myocyte regeneration, Cardiogenic Shock, Cardiology, Cardiometabolic Syndrome, CHF, Content Curation, Coronary artery disease, Coronary stent, Curation methodology, Drug-eluting stents, gene expression, Hypertension, myocardial hypertrophy, nitric oxide, Nitric oxide synthase, RNA, Stem cell on January 1, 2014| 1 Comment »

The Cost to Value Conundrum in Cardiovascular Healthcare Provision

Author: Larry H. Bernstein, MD, FCAP

I write this introduction to Volume 2 of the e-series on Cardiovascular Diseases, which curates the basic structure and physiology of the heart, the vasculature, and related structures, e.g., the kidney, with respect to:

1. Pathogenesis
2. Diagnosis
3. Treatment

Curation is an introductory portion to Volume Two, which is necessary to introduce the methodological design used to create the following articles. More needs not to be discussed

about the methodology, which will become clear, if only that the content curated is changing based on success or failure of both diagnostic and treatment technology availability, as well as the systems needed to support the ongoing advances. Curation requires:

- meaningful selection,
- enrichment, and
- sharing combining sources and
- creation of new synnthesis

Curators have to create a new perspective or idea on top of the existing media which supports the content in the original. The curator has to select from the myriad upon myriad options available, to re-share and critically view the work. A search can be overwhelming in size of the output, but the curator has to successfully pluck the best material straight out of that noise.

Part 1 is a highly important treatment that is not technological, but about the system now outdated to support our healthcare system, the most technolog-ically advanced in the world, with major problems in the availability of care related to economic disparities. It is not about technology, per se, but about how we allocate healthcare resources, about individuals' roles in a not full list of lifestyle maintenance options for self-care, and about the important advances emerging out of the Affordable Care Act (ACA), impacting enormously on Medicaid, which depends on state-level acceptance, on community hospital, ambulatory, and home-care or hospice restructuring, which includes the reduction of management overhead by the formation of regional healthcare alliances, the incorporation of physicians into hospital-based practices (with the hospital collecting and distributing the Part B reimbursement to the physician, with "performance-based" targets for privileges and payment – essential to the success of an Accountable Care Organization (AC)). One problem that ACA has definitively address is the elimination of the exclusion of patients based on preconditions. One problem that has been left unresolved is the continuing existence of private policies that meet financial capabilities of the contract to provide, but which provide little value to the "purchaser" of care. This is a holdout that persists in for-profit managed care as an option. A physician response to the new system of care, largely fostered by a refusal to accept Medicaid, is the formation of direct physician-patient contracted care without an intermediary.

In this respect, the problem is not simple, but is resolvable. A proposal for improved economic stability has been prepared by Edward Ingram. A concern for American families and businesses is substantially addressed in a macroeconomic design concept, so that financial services like housing, government, and business finance, savings and pensions, boosting confidence at every level giving everyone a better chance of success in planning their personal savings and lifetime and business finances.

http://macro-economic-design.blogspot.com/p/book.html

Part 2 is a collection of scientific articles on the current advances in cardiac care by the best trained physicians the world has known, with mastery of the most advanced vascular instrumentation for medical or surgical interventions, the latest diagnostic ultrasound and imaging tools that are becoming outdated before the useful lifetime of the capital investment has been completed. If we tie together Part 1 and Part 2, there is ample room for considering clinical outcomes based on individual and organizational factors for best performance. This can really only be realized with considerable improvement in information infrastructure, which

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has miles to go. Why should this be? Because for generations of IT support systems, they are historically focused on billing and have made insignificant inroads into the front-end needs of the clinical staff.

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MicroRNA in Serum as Biomarker for Cardiovascular Pathologies: acute myocardial infarction, viral myocarditis, diastolic dysfunction, and acute heart failure

Posted in Biological Networks, Gene Regulation and Evolution, Cardiomyopathy, Cardiovascular Research, Cell Biology, Signaling & Cell Circuits, Chemical Genetics, Computational Biology/Systems and Bioinformatics, Frontiers in Cardiology and Cardiovascular Disorders, Genome Biology, Genomic Testing: Methodology for Diagnosis, Medical and Population Genetics, Molecular Genetics &

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Pharmaceutical, Myocardial metabolism, Myocardial ischemia, Myocardial adenine nucleotide metabolism, Origins of Cardiovascular Disease, Personalized and Precision Medicine & Genomic Research, Population Health Management, Genetics & Pharmaceutical, Translational Science, tagged Cardiology, Cardiovascular disease, MicroRNA, Takeshi Kimura on December 12, 2013| 2 Comments »

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MicroRNA in Serum as Biomarker for Cardiovascular Pathologies: acute myocardial infarction, viral myocarditis, diastolic dysfunction, and acute heart failure

Reporter: Aviva Lev-Ari, PhD, RN

Increased MicroRNA-1 and MicroRNA-133a Levels in Serum of Patients With Cardiovascular Disease Indicate Myocardial Damage

Yasuhide Kuwabara, MD, Koh Ono, MD, PhD, Takahiro Horie, MD, PhD, Hitoo Nishi, MD, PhD, Kazuya Nagao, MD, PhD, Minako Kinoshita, MD, PhD, Shin Watanabe, MD, PhD, Osamu Baba, MD, Yoji Kojima, MD, PhD, Satoshi Shizuta, MD, Masao Imai, MD,Toshihiro Tamura, MD, Toru Kita, MD, PhD and Takeshi Kimura, MD, PhD

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Abstract

Background—Recently, elevation of circulating muscle-specific microRNA (miRNA) levels has been reported in patients with acute myocardial infarction. However, it is still unclear from which part of the myocardium or under what conditions miRNAs are released into circulating blood. The purpose of this study was to identify the source of **elevated levels of circulating miRNAs** and their function in cardiovascular diseases.

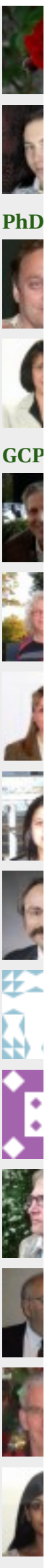
Conclusions—These results suggest that elevated levels of **circulating miRNA-133a** in patients with cardiovascular diseases originate mainly from the injured myocardium. Circulating miR-133a can be used as a marker for cardiomyocyte **death**, and it may have functions in cardiovascular diseases.

SOURCE:

Circulation: Cardiovascular Genetics. 2011; 4: 446-454

Published online before print June 2, 2011,

doi: 10.1161/ CIRCGENETICS.110.958975



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Ischemic Stable CAD (FFR): In >5000 Patients – Medical Therapy and PCI no difference in End Point: Meta-Analysis of Contemporary Randomized Clinical Trials

Posted in Atherogenic Processes & Pathology, Cardiac and Cardiovascular Surgical Procedures, Cardiovascular Research, Frontiers in Cardiology and Cardiovascular Disorders, Medical Devices R&D and Inventions, Myocardial metabolism, Myocardial ischemia, Myocardial adenine nucleotide metabolism, Origins of Cardiovascular Disease, PCI, Pharmacotherapy of Cardiovascular Disease, Stents & Tools, tagged CAD, Cardiology, Cardiovascular disease, Coronary artery disease, Ischemia, Percutaneous coronary intervention on December 3, 2013| Leave a Comment »

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Ischemic Stable CAD: Medical Therapy and PCI no difference in End Point: Meta-Analysis of Contemporary Randomized Clinical Trials

Reporter: Aviva Lev-Ari, PhD, RN

SOURCE

Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: A collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med* 2013; DOI:10.1001/jamainternmed.2013.12855. Available at:http://www.jamainternalmedicine.com.

Heartwire

PCI No Benefit Over Medical Therapy in Ischemic Stable CAD

Shelley Wood

December 02, 2013

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- #41: The ISCHEMIA trial on optimal care for patients with stable coronary disease with Dr Judith Hochman
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DRUG & REFERENCE INFORMATION

- Percutaneous Coronary Intervention
- Comparison of Revascularization Procedures in Coronary Artery Disease
- Cardiogenic Shock

NEW YORK, NY — A new analysis is calling into question the de facto rationale for many of the revascularization procedures taking place today, at least in patients with stable coronary artery disease[1]. In a meta-analysis of more than 5000 patients, PCI was no better than medical therapy in patients with documented ischemia by stress testing or fractional flow reserve (FFR).

"Cardiology has a long history of finding a marker of a bad outcome and treating that marker of that bad outcome as if it were the *cause* of the bad outcome," senior author on the study, **Dr David Brown** (State University of New York [SUNY]–Stony Brook School of Medicine), told **heart*wire*** . In the case of proceeding to PCI on the basis of documented ischemia, that stems from evidence that patients with ischemia have a worse prognosis than patients who don't."It has gotten to the point that a positive stress test [is the gateway] to doing an intervention, even if the ischemia is not in the same ischemic territory as the vessel being treated," he said. "The medical/industrial complex in cardiology is now focused on finding and treating ischemia, and I think that's not justified, and these data suggest that that's not justified."

Brown and colleagues, with first author **Dr Kathleen Stergiopoulus** (SUNY–Stony Brook School of Medicine), reviewed the literature for randomized clinical trials of PCI and medical therapy for stable CAD conducted over the past 40 years, ultimately including five trials of 5286 patients. These were a small German trial published in 2004, plus **MASS II** , **COURAGE** , **BARI 2D** , and **FAME 2** . In all, 4064 patients had myocardial ischemia documented by exercise, nuclear or echo stress imaging, or FFR.

Over a median follow-up of five years, mortality, nonfatal MI, unplanned revascularization, and angina were no different between patients treated medically vs those treated with PCI.

Odds Ratio, PCI vs Medical Therapy

Outcome	Odds ratio	95% CI
Death	0.90	0.71–1.16
Nonfatal MI	1.24	0.99–1.56
Unplanned revascularization	0.64	0.35–1.17
Angina	0.91	0.57–1.44

"These findings are unique in that this is the first meta-analysis to our knowledge limited to patients with documented, objective findings of myocardial ischemia, almost all of whom underwent treatment with intracoronary stents and disease-modifying secondary-prevention therapy," Stergiopoulus et al write.

The findings, they continue, "strongly suggest that the relationship between ischemia and mortality is not altered or ameliorated by catheter-based revascularization of obstructive, flow-limiting coronary stenosis."

To **heart*wire*** , Brown pointed out that their analysis could not separate out patients who had small amounts of ischemia from those with larger ischemic territories. "Maybe that's where the differentiating factor will be," he acknowledged, adding that the 8000-patient **ISCHEMIA** trial,

still ongoing, will hopefully yield some insights.

Current practice, however, is to check for ischemia and to proceed with catheterization and, usually, revascularization when ischemia is confirmed by stress testing or during FFR. "But if that doesn't improve outcomes, why are we doing it?" Brown asked. "We think that needs to be rethought."

Information from Industry

Commenting on the study for **heart*wire*** , **Dr Peter Berger**(Geisinger Health System, Danville, PA) pointed out: "There is no question that PCI is more effective than medical therapy for relief of symptoms: the more severe the angina and the more active the patient, the greater the superiority of PCI." And, as Berger noted, most of the studies included in this analysis documented ischemia but did not report on the frequency or severity of angina at baseline.

That said, "Patients with minimal angina—and certainly those with silent ischemia but no angina—are unlikely to have a significantly greater reduction of symptoms with PCI, and PCI is rarely beneficial in such patients."

Moreover, Berger continued, it has been clearly established that PCI does not reduce the risk of death or MI in most such patients.

"I very much agree with the authors, however, that just because more severe ischemia has been shown to be associated with a worse long-term prognosis, reducing the ischemic burden ought not be assumed to reduce the likelihood of death or MI. In most such patients, it does not."

Stergiopoulos and Brown had no disclosures. Disclosures for the coauthors are listed in the paper.

SOURCE

http://www.medscape.com/viewarticle/815234?nlid=40823_2105&src=wnl_edit_medp_card&uac=93761AJ&spon=2

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Intracoronary Transplantation of Progenitor Cells after Acute MI

Posted in Stem Cells for Regenerative Medicine, Technology Transfer: Biotech and Pharmaceutical, tagged 3 months post MI, BMC, Cardiac muscle, Cardiology, Clinical Trials, CPC, Ejection Fraction, Heart Failure, LV function, myocardial infarction, Progenitor cell, progenitor cells, Ventricle (heart) on November 2, 2013| 4 Comments »

Intracoronary Transplantation of Progenitor Cells after Acute MI

Curators: Larry H. Bernstein, MD, FCAP and Aviva Lev-Ari, PhD, RN

Transcoronary Transplantation of Progenitor Cells after Myocardial Infarction

Birgit Assmus, M.D., Jörg Honold, M.D., Volker Schächinger, M.D., Martina B. Britten, M.D., Ulrich Fischer-Rasokat, M.D., et al.
From the Division of Cardiology and Mo lecular Cardiology, Department of Medi cine III (B.A., J.H., V.S., M.B.B., U.F.-R., R.L., C.T., K.P., S.D., A.M.Z.), Division of He matology, Department of Medicine II (H.M.), and the Department of Diagnos tic and Interventional Radiology (N.D.A.), Johann Wolfgang Goethe University; and the Institute for Transfusion Medicine and Immunohematology, Red Cross Blood Donor Service, Baden–Württem-berg–Hessen (T.T.) — both in Frankfurt, Germany.

N Engl J Med 2006;355:1222-32.

Background

Pilot studies suggest that intracoronary transplantation of progenitor cells derived from bone marrow (BMC) or circulating blood (CPC) may improve left ventricular function after acute myocardial infarction. The effects of cell transplantation in patients with healed myocardial infarction are unknown.

METHODS

After an initial pilot trial involving 17 patients, we randomly assigned, in a controlled crossover study, **75 patients with stable ischemic heart disease who had had a myo cardial infarction at least 3 months previously to receive either no cell infusion (23 patients) or infusion of CPC (24 patients) or BMC (28 patients)** into the patent coro nary artery supplying the most dyskinetic left ventricular area. The patients in the control group were

- subsequently randomly assigned to receive CPC or BMC, and
- the patients who initially received BMC or CPC crossed over to receive CPC or BMC, respectively, at 3 months' follow-up.

RESULTS

The absolute change in left ventricular ejection fraction was significantly greater among patients receiving BMC (+2.9 percentage points) than among those receiving CPC (−0.4 percentage point, P = 0.003) or no infusion (−1.2 percentage points, P<0.001). The increase in global cardiac function was related to significantly

- en hanced regional contractility in the area targeted by intracoronary infusion of BMC.

The crossover phase of the study revealed that **intracoronary infusion of BMC was associated with a significant increase in global and regional left ventricular func tion**,

regardless of whether patients crossed over from control to BMC or from CPC to BMC.

CONCLUSIONS

Intracoronary infusion of progenitor cells is safe and feasible in patients with healed myocardial infarction. Transplantation of BMC is associated with moderate but significant improvement in the left ventricular ejection fraction after 3 months. (ClinicalTrials.gov number, NCT00289822.)

Introduction

HRONIC HEART FAILURE IS COMMON, and its prevalence continues to increase.[1] Ischemic heart disease is the principal cause of heart failure.[2] Although myocardial salvage due to early reperfusion therapy has significantly re duced early mortality rates,[3]

- postinfarction heart failure resulting from ventricular remodeling re mains a problem.[4]

One possible approach to **re versing postinfarction heart failure**is

- enhance ment of the regeneration of cardiac myocytes as well as
- stimulation of neovascularization within the infarcted area.

Initial clinical pilot studies have suggested that

- intracoronary infusion of pro genitor cells is feasible and may
- beneficially af fect postinfarction remodeling processes in pa tients with acute myocardial infarction.[5-9]

However, it is currently unknown whether such a treatment strategy may also be associated with

- improvements in cardiac function in patients with persistent left ventricular dysfunction due to healed myocardial infarction with established scar formation.

Therefore, in the prospective TOPCARE-CHD (Transplantation of Progenitor Cells and Recovery of LV [Left Ventricular] Function in Patients with Chronic Ischemic Heart Disease) trial, we inves tigated

- whether intracoronary infusion of pro genitor cells into the infarct-related artery at least 3 months after myocardial infarction improves global and regional left ventricular function.

Patient Outcome Criteria

The primary end point of the study was the absolute change in **global left ventricular ejection fraction (LVEF)** as measured by **quantitative left ventricular angiography** 3 months after cell infu sion. Secondary end points included **quantitative variables relating to the regional left ventricular function of the target area**, as well as **left ven tricular volumes derived from serial left ventric ular angiograms**. In addition, functional status was assessed by NYHA classification. Finally, **event-free survival** was defined as freedom from death, myocardial

infarction, stroke, or rehospi talization for worsening heart failure. Causes of rehospitalization during follow-up were verified by review of the discharge letters or charts of hospital stays.

DETECTION OF VIABLE MYOCARDIUM

All patients underwent low-dose dobutamine stress echocardiography, combined thallium sin gle-photon-emission computed tomography and [^{18}F]fluorodeoxyglucose positron-emission tomog raphy, or both, as previously described.[6] It was pos sible to analyze regional left ventricular viability in 80 patients (87%).

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

A total of 92 patients were enrolled in the study. Of these, 35 patients received BMC as their ini tial treatment (in phases 1 and 2 of the trial), 34 patients received CPC (in phases 1 and 2), and 23 patients received no intracoronary cell infu sion (in phase 2, as the control group). Table 1 illustrates that the three groups of patients were well matched.

EFFECTS OF PROGENITOR-CELL INFUSION

Quantitative Characteristics of Left Ventricular Function

Patients with an adverse clinical event (six), sub total stenosis of the target vessel at follow-up (three), an intraventricular thrombus precluding performance of left ventricular angiography (one), or atrial flutter or fibrillation at follow-up (one) were excluded from the exploratory analysis. In addition, of the 81 eligible patients, left ventricu lar angiograms could not be quantitatively ana lyzed in 4 because of inadequate contrast opaci-fication, in 1 because of ventricular extrasystoles, and in 4 because of the patients' refusal to un dergo invasive follow-up. Thus, a total of 72 of 81 serial paired left ventricular angiograms were available for quantitative analysis (28 in the BMC group, 26 in the CPC group, and 18 in the control group).

Table 2 summarizes the angiographic charac teristics of the 75 patients included in the ran domized phase of the study. At baseline, the three groups did not differ with respect to global LVEF, the extent or magnitude of regional left ventricu lar dysfunction, left ventricular volumes, or stroke volumes.

The absolute change in global LVEF from base line to 3 months did significantly differ among the three groups of patients. Patients receiving BMC had a significantly larger change in LVEF than patients receiving CPC ($P = 0.003$) and those in the control group ($P<0.001$). Similar results were ob tained when patients from the first two phases of the study (the pilot phase and the randomized phase) were pooled. The results did not differ when patients without evidence of viable myo cardium before inclusion were analyzed sepa rately. The change in LVEF was −0.3±3.4 percent age points in the control group (9 patients), +0.4±3.0 percentage points in the CPC group (18 patients), and +3.7±4.0 percentage points in the BMC group (18 patients) ($P = 0.02$ for the com parison with the control group and $P = 0.02$ for the comparison with the CPC group).

In the subgroup of 35 patients who underwent serial assessment of left ventricular function by MRI, MRI-derived global LVEF increased signifi cantly, by 4.8±6.0% ($P = 0.03$) among those

receiv ing BMC (11 patients) and by 2.8±5.2% (P = 0.02) among those receiving CPC (20 patients), where as no change was observed in 4 control patients (P = 0.14). Thus, MRI-derived assessment of left ventricular function further corroborated the re sults obtained from the total patient population.

Analysis of regional left ventricular function revealed that BMC treatment significantly in creased contractility in the center of the left ven tricular target area (Table 2). Likewise, MRI-derived regional analysis of left ventricular function re vealed that the number of hypocontractile seg ments was significantly reduced, from 10.1±3.6 to 8.7±3.6 segments (P = 0.02), and the number of normocontractile segments significantly in creased, from 3.8±4.5 to 5.4±4.6 segments (P = 0.01), in the BMC group, whereas no significant changes were observed in the CPC group. MRI-derived infarct size, as measured by late enhance ment volume normalized to left ventricular mass, remained constant both in the CPC group (25± 18% at baseline and 23±14% at 3 months,13 patients) and in the BMC group (20±10% at both time points, 9 patients). Thus, taken together, the data suggest that intracoronary infusion of BMC is associated with significant improvements in global and regional left ventricular contractile function among patients with persistent left ven tricular dysfunction due to prior myocardial in farction.

To identify independent predictors of improved global LVEF, a stepwise multivariate regression analysis was performed; it included classic deter minants of LVEF as well as various baseline characteristics of the three groups (Table 3). The multivariate analysis identified the type of pro genitor cell infused and the baseline stroke vol ume as the only statistically significant indepen dent predictors of LVEF recovery.

Functional Status

The functional status of the patients, as assessed by NYHA classification, improved significantly in the BMC group (from 2.23±0.6 to 1.97±0.7, P = 0.005). It did not improve significantly either in the CPC group (class, 2.16±0.8 at baseline and 1.93±0.8 at 3 months; P = 0.13) or in the control group (class, 1.91±0.7 and 2.09±0.9, respectively; P = 0.27).

RANDOMIZED CROSSOVER PHASE

Of the 24 patients who initially were randomly assigned to CPC infusion, 21 received BMC at the time of their first follow-up examination. Likewise, of the 28 patients who initially were randomly assigned to BMC infusion,

- 24 received CPC after 3 months.

Of the 23 patients of the control group, 10 patients received CPC and 11 received BMC at their reexamination at 3 months (Fig. 1). As illustrated in Figure 2, regardless of whether patients received BMC as initial treatment, as crossover treatment after CPC infusion, or as crossover treatment after no cell infusion,

- glob al LVEF increased significantly **after infusion of BMC**. In contrast,
- CPC treatment did not significantly alter LVEF when given either before or after BMC.

Thus, **the intrapatient comparison of the dif ferent treatment strategies not only documents the superiority of intracoronary infusion of BMC over the infusion of CPC for improving**

global left ventricular function, but also corroborates our findings in the analysis of data according to initial treatment assignment. The

- preserved im provement in cardiac function observed among patients who initially received BMC treatment and
- then crossed over to CPC treatment demon strates that the**initially achieved differences in cardiac function persisted for at least 6 months after intracoronary infusion of BMC**.

Table 1. Baseline Characteristics of the Patients.* (not copied)

Table 2. Quantitative Variables Pertaining to Left Ventricular Function, as Assessed by Left Ventricular Angiography.*

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Figure 2. Absolute Change in Quantitative Global Left Ventricular Ejection Fraction (LVEF) during the Crossover Phase of the Trial.

Data at 3 and 6 months are shown for all patients crossing over from BMC to CPC infusion (18 patients), from CPC to BMC infusion
(18 patients), and from no cell infusion to either CPC infusion (10 patients) or BMC infusion (11 patients). I bars represent standard
errors.

Table 3. Stepwise Linear Regression Analysis for Predictors of Improvement in Global Left Ventricular Ejection Fraction.*

Variable	Nonstandardized Coefficient B	95% CI for B	P Value
Treatment group	1.49	0.53 to 2.46	0.003
Baseline stroke volume	−0.13	−0.22 to −0.05	0.002
No. of cardiovascular risk factors			0.76
Time since most recent MI			0.48
Concomitant PCI			0.60
Age			0.82
Baseline ejection fraction			0.72
Baseline end-diastolic volume			0.88

* Values are shown only for significant differences. MI denotes myocardial infarc tion, and PCI percutaneous coronary intervention. For the overall model, the ad justed R^2 was 0.29; P<0.001 by analysis of variance.

DISCUSSION

Intrapatient comparison in the crossover phase of the trial rules out the possibility that differences in the patient populations studied may have affected outcomes. However, the mechanisms involved in mediating improved contractile function after intracoronary progenitor-cell infusion are not well understood.

Experimentally, although there is no definitive proof that cardiac myocytes may be regenerated, BMC were shown to contribute to functional re covery of left ventricular contraction when in jected into freshly infarcted hearts,[13-15] whereas CPC profoundly stimulated ischemia-induced neovascularization.[16,17] Both cell types were shown to prevent cardiomyocyte apoptosis and reduce the development of myocardial fibrosis and there by improve cardiac function after acute myocar dial infarction.[18,19] Indeed, in our TOPCARE-AMI (Transplantation of Progenitor Cells and Regen eration Enhancement in Acute Myocardial Infarc tion) studies,[6,7,9] **intracoronary infusion of CPC was associated with functional improvements similar to those found with the use of BMC im mediately after myocardial infarction**. In the cur rent study, however, which involved patients who had had a myocardial infarction at least 3 months before therapy,

- transcoronary adminis tration of CPC was significantly inferior to administration of BMC in altering global left ven tricular function.

CPC obtained from patients with chronic ischemic heart disease **show pro found functional impairments,[20,21] which might limit their recruitment, after intracoronary infu sion, into chronically reperfused scar tissue many months or years after myocardial infarction**. Thus, additional studies in which larger numbers of functionally enhanced CPC are used will be re quired to increase the response to intracoronary infusion of CPC.

The magnitude of the improvement after in-tracoronary infusion of BMC, with absolute increases in global LVEF of approximately 2.9 percentage points according to left ventricular angiography and 4.8 percentage points accord ing to MRI, was modest. However, it should be noted that the improvement in LVEF occurred in the setting of full conventional pharmacologic treatment: more than 90% of the patients were receiving beta-blocker and angiotensin-convert-ing–enzyme inhibitor treatment. Moreover, results from trials of contemporary reperfusion for the treatment of acute myocardial infarction, which is regarded as the most effective treatment strat egy for improving left ventricular contractile per formance after ischemic injury, have reported in creases in global LVEF of 2.8% (in the CADILLAC [Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications] trial) and 4.1% (in the ADMIRAL [Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Fol low-up] trial).22,23

The number of patients, as well as the dura tion of follow-up, is not sufficient to address the question of whether the moderate improvement in LVEF associated with one-time intracoronary BMC infusion is associated with reduced mortal ity and morbidity among patients with heart fail ure secondary to previous myocardial infarction. We conclude that **intracoronary infusion of BMC is associated with persistent improvements in regional and global left ventricular function and improved functional status among patients who have**

had a myocardial infarction at least 3 months previously. Given the reasonable short-term safety profile of this therapeutic ap proach, studies on a larger scale are warranted to examine its potential effects on morbidity and mortality among patients with postinfarction heart failure.

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Three-Dimensional Fibroblast Matrix Improves Left Ventricular Function Post MI

Posted in Stem Cells for Regenerative Medicine, Technology Transfer: Biotech and Pharmaceutical, tagged 3-D fibrobast patch, AZ, cardiac damage, Cardiology, cell transplant, improvement of heart function, Left ventricle, myocardial infarction, Tucson on November 2, 2013| 2 Comments »

Three-Dimensional Fibroblast Matrix Improves Left Ventricular Function post MI

Curators: Larry H. Bernstein, MD. FCAP and Aviva Lev-Ari, PhD, RN

Implantation of a Three-Dimensional Fibroblast Matrix Improves Left Ventricular Function and Blood Flow After Acute Myocardial Infarction

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Cell Transplant. 2009 ; 18(3): 283–295. http://dx.doi.org/10.3727/096368909788535004

Abstract

This study was designed to determine **if a viable biodegradable three-dimensional fibroblast construct (3DFC) patch implanted on the left ventricle after myocardial infarction (MI) improves left ventricular (LV) function and blood flow.** We ligated the left coronary artery of adult male Sprague-Dawley rats and implanted the 3DFC at the time of the infarct. Three weeks after MI, the 3DFC improved LV systolic function by increasing ($p < 0.05$) ejection fraction (37 ± 3% to 62 ± 5%), increasing regional systolic displacement of the infarcted wall (0.04 ± 0.02 to 0.11 ± 0.03 cm), and shifting the passive LV diastolic pressure volume relationship toward the pressure axis. The 3FDC improved LV remodeling by decreasing ($p < 0.05$) LV end-systolic and end-diastolic diameters with no change in LV systolic pressure. The 3DFC did not change LV end-diastolic pressure (LV EDP; 25 ± 2 vs. 23 ± 2 mmHg) but the addition of captopril (2mg/L drinking water) lowered ($p < 0.05$) LV EDP to 12.9 ± 2.5 mmHg and shifted the pressure–volume relationship toward the pressure axis and decreased ($p < 0.05$) the LV operating end-diastolic volume from 0.49 ± 0.02 to 0.34 ± 0.03 ml. The 3DFC increased myocardial blood flow to the infarcted anterior wall after MI over threefold ($p < 0.05$). This biodegradable 3DFC patch improves LV function and myocardial blood flow 3 weeks after MI. This is a potentially new approach to cell-based therapy for heart failure after MI.

Three-Dimensional Fibroblast Patch

Our hypothesis is that the lack of survival of new cells directly injected into the heart is related, in part, to an inadequate blood supply and inadequate matrix support for the new cells. The injected cells are fragile, resulting in cell aggregation due to lack of physical support for the cells to attach to the tissue extracellular matrix. This three-dimensional scaffold offers a potential solution to the problem of an inadequate support structure. While injection of passive materials has been proposed to improve EF potentially by decreasing wall stress (11,35), the 3DFC provides a viable cell matrix that supports new blood vessel growth (15,16). This viable cellular matrix is important because in addition to providing a new support structure for the damaged heart, we also need to create a mature blood supply such that new viable cardiac muscle can be organized in parallel forming physical and neural connections that will conduct electrical

signals and create synchronized contractions. Investigators have proposed that the ideal scaffold structure for the heart would consist mainly of highly interconnected pores with a diameter of at least 200 μm, the average size of a capillary, to permit blood vessel penetration and cell interactions (5).

The 3DFC is a viable construct composed of a matrix embedded with human newborn dermal fibroblasts cultured in vitro onto a bioabsorbable mesh to produce living, metabolically active tissue (15,16) (see Fig. 1 and Fig 2). As the fibroblasts proliferate across the mesh, they secrete human dermal collagen, fibronectin, and glycosaminoglycans (GAGs), embedding themselves in a self-produced dermal matrix. The fibroblast cells produce angiogenic growth factors: vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), and angiopoietin-1. The construct is grown in medium supplemented with serum and ascorbate; at harvest, the medium is replaced with a 10% DMSO-based cryoprotectant, the tissue is frozen and stored at −70°C. This cryopreservation and rewarming technique has been extensively studied to ensure viability of the patch. Although the mechanisms of action of the 3DFC are not completely understood, new blood vessel growth has been documented previously in SCID mice (15).

Previous work using the 3DFC as a patch for the infarcted heart in SCID mice showed histological evidence of new blood vessel growth and improvements in global LV function using a conductance catheter (16). Our data show increases in myocardial blood flow in the infarcted heart, confirming that these blood vessels are functional and that they connect to the native myocardium. We used echocardiography to document improvements in global and regional LV function. The improvements in regional LV function are important because recent work suggests that the injection of passive materials alone may be enough to reduce wall stress and increase global EF (35). In order to prove that cell-based therapy is affecting more than a passive response, the point has been made that it is necessary to be able to define regional changes in the area of the infarcted myocardium (11). We have done this using echocardiography to document that the 3DFC increases systolic displacement of the infarcted regional anterior wall (Fig. 5). Although the mechanism of action of the 3DFC has not been completely delineated, the viable fibroblasts secrete a number of growth factors, thus providing a paracrine effect to stimulate new blood vessel growth. The vicryl mesh is biodegradable such that, with dissolution, the new blood vessel growth is in the previously damaged myocardium. The most likely explanation for the improvements in regional systolic displacement of the anterior wall is that the increases in myocardial blood flow in the border zone results in recruitment of hibernating or stunned cardiac myocytes.

The fact that the 3DFC is viable with fibroblasts implanted on a mesh is important. There are data showing that inert biodegradable patches are beneficial in treating heart failure. In our laboratory we have shown that an inert biodegradable collagen patch placed on the rat heart after a nontransmural MI improves LV function and prevents adverse LV remodeling (10). There are clinical trials with a collagen type 1 matrix seeded with autologous bone marrow cells in patients undergoing coronary artery bypass surgery (4). The best known implanted mechanical constraint device is the Acorn Corp Cap device; it decreases LV size but does not cause constrictive physiology (22). There are no blood flow studies with the Acorn device. There is a recent report using an inert biodegradable polyester urethane cardiac patch applied to rats 2 weeks after coronary ligation where the LV cavity size does not change but fractional area

change increases and compliance improves; there are no blood flow data in this report (6).

Application of a Patch as an Alternative to Direct Cell Injection

The use of a biodegradable patch that provides a support structure allowing new cells to attach and grow in a damaged heart is a possible alternative to the current approach of direct cell injection for cell-based therapy. Not only are the results from current clinical trials of cell-based therapy disappointing, the approach used in these trials is cumbersome, requiring harvesting bone marrow and a repeat cardiac catheterization with infarct artery reocclusion to reinject purified autologous mononuclear cells into the coronary arteries. Another problem is the recent report that intracoronary delivery of bone marrow cells results in damage to the coronary artery with luminal loss in the infarct related artery (20). These data suggest that we need new options for cell-based therapy for heart failure.

The translational aspect of this work is important; there is potential for clinical application of this 3DFC patch. At present there are two ongoing phase I clinical trials using the 3DFC; the first is a pilot trial in patients applying the 3DFC patch at the time of coronary artery bypass surgery when the surgeon cannot place a graft to a area of viable myocardium. This trial is designed to determine if the 3DFC increases myocardial perfusion to an area that the surgeon could not graft. While in this clinical study the 3DFC patch is placed with the chest open, two cases have been done with a minimally invasive approach using a modified video-assisted thorascopic surgery VATS procedure. The second trial is in patients getting a left ventricular assist device (LVAD). The 3DFC is applied at the time of LVAD placement and, upon LVAD removal, histology is done on the area of 3DFC placement in order to examine for evidence of angiogenesis.

Summary

We report improvements in myocardial blood flow, regional and global LV function, and partial reversal of LV remodeling using a viable three-dimensional fibroblast patch implanted in rats at the time of an acute MI. This patch provides a support structure that allows cells to grow into the damaged heart and creates new blood vessel growth, resulting in improved blood flow. With the limited success of direct cell injection into the heart, the 3DFC represents a new approach to cell-based therapy for heart failure.

Figures

Figure 1. Scanning electron micrograph of the 3DFC patch.

The vicryl fibers are "tube-like" structures. The fibroblasts look like irregular structures with long appendages that span from one vicryl fiber to another.

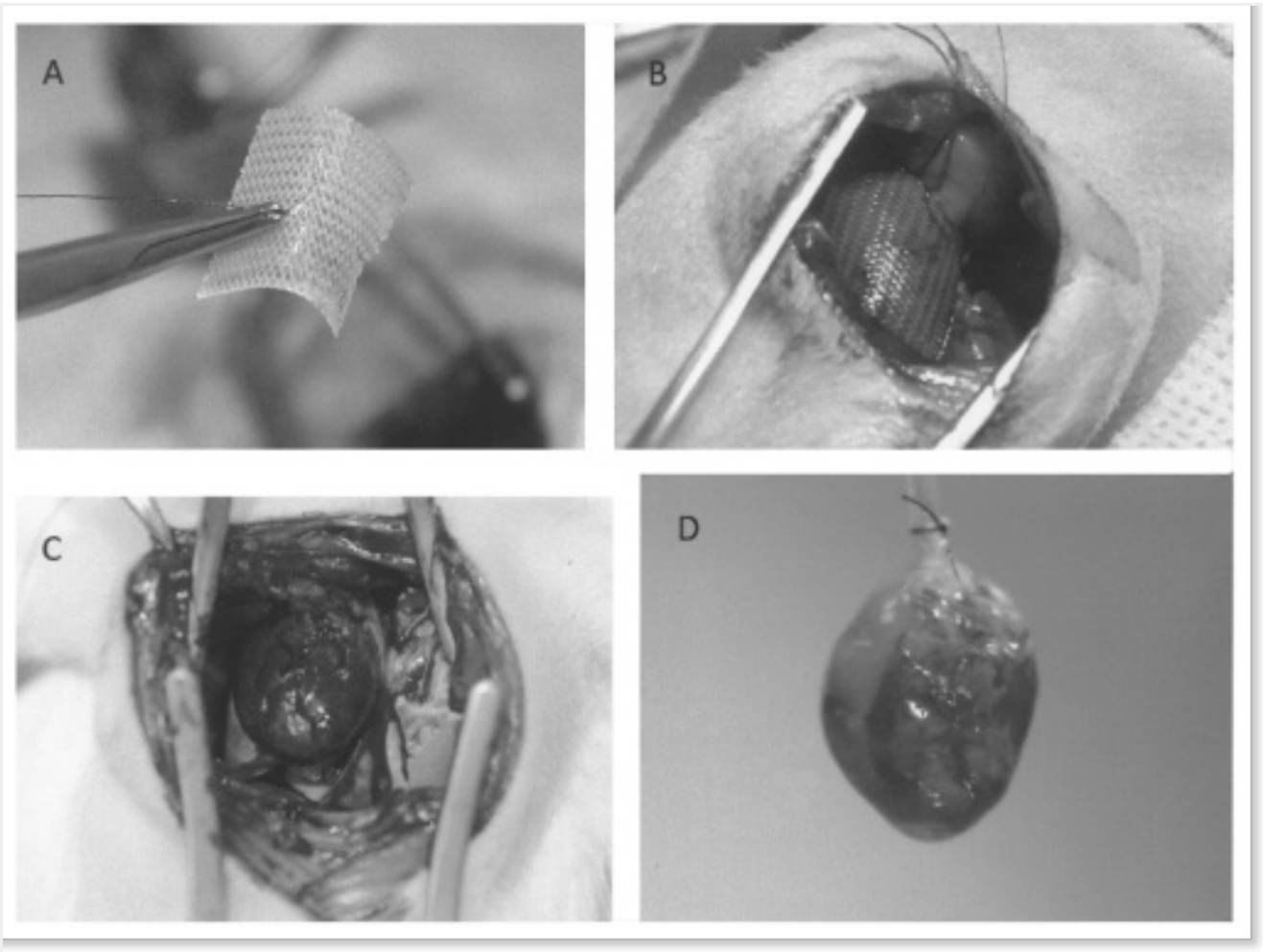


Figure 2.

(A) Three-dimensional fibroblast culture (3DFC) prior to implantation; the suture in the middle of the patch is used to attach the 3DFC to the left ventricle. (B) 3DFC at the time of implantation on the infarcted left ventricle. (C) 3DFC at 3 weeks after

myocardial infarction. Note that the 3DFC is well integrated and attached to the infarcted wall. (D) 3DFC in a perfused heart preparation at 3 weeks after myocardial infarction. As note above, the 3DFC is well integrated into the infarcted wall and the suture is easily visible.

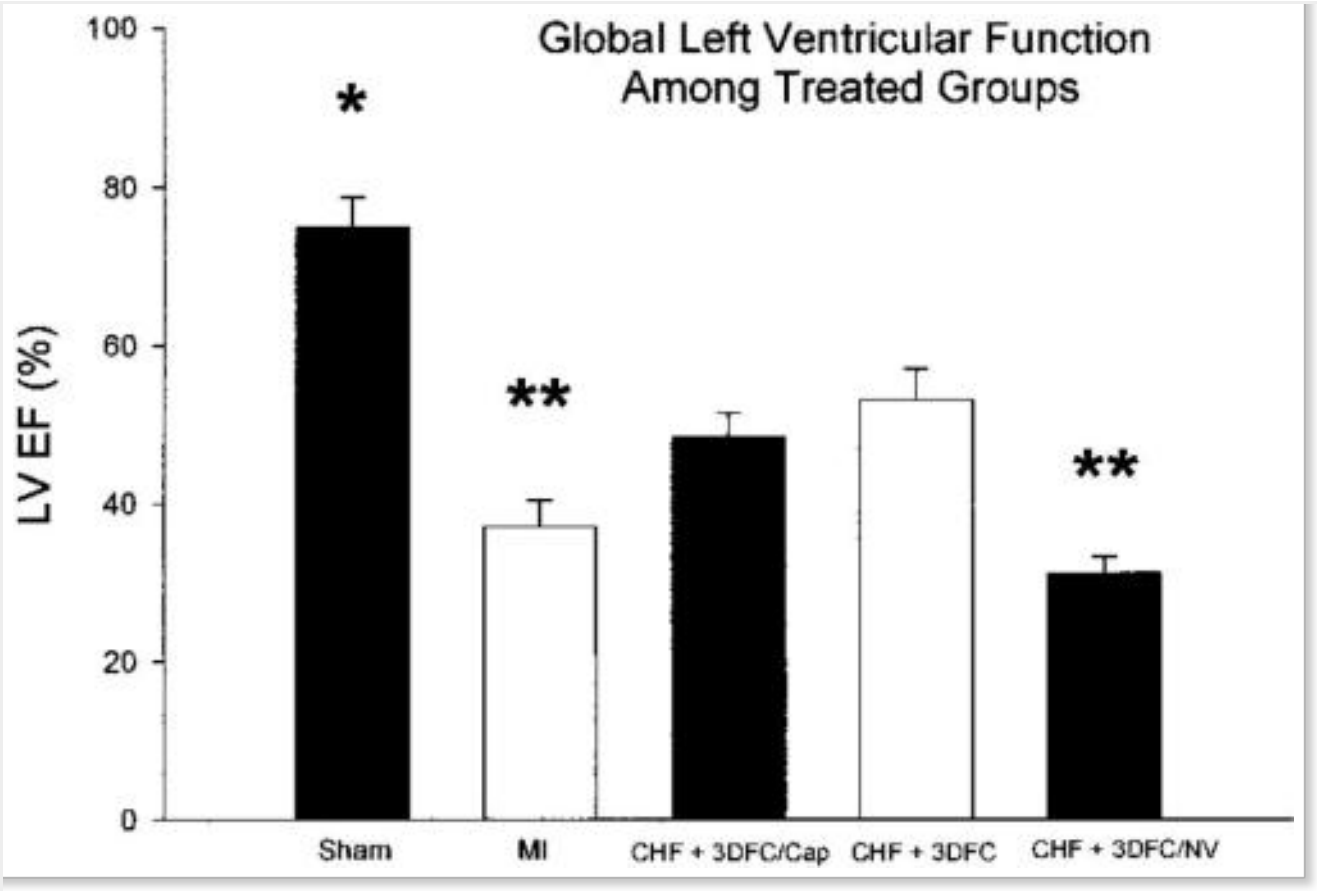
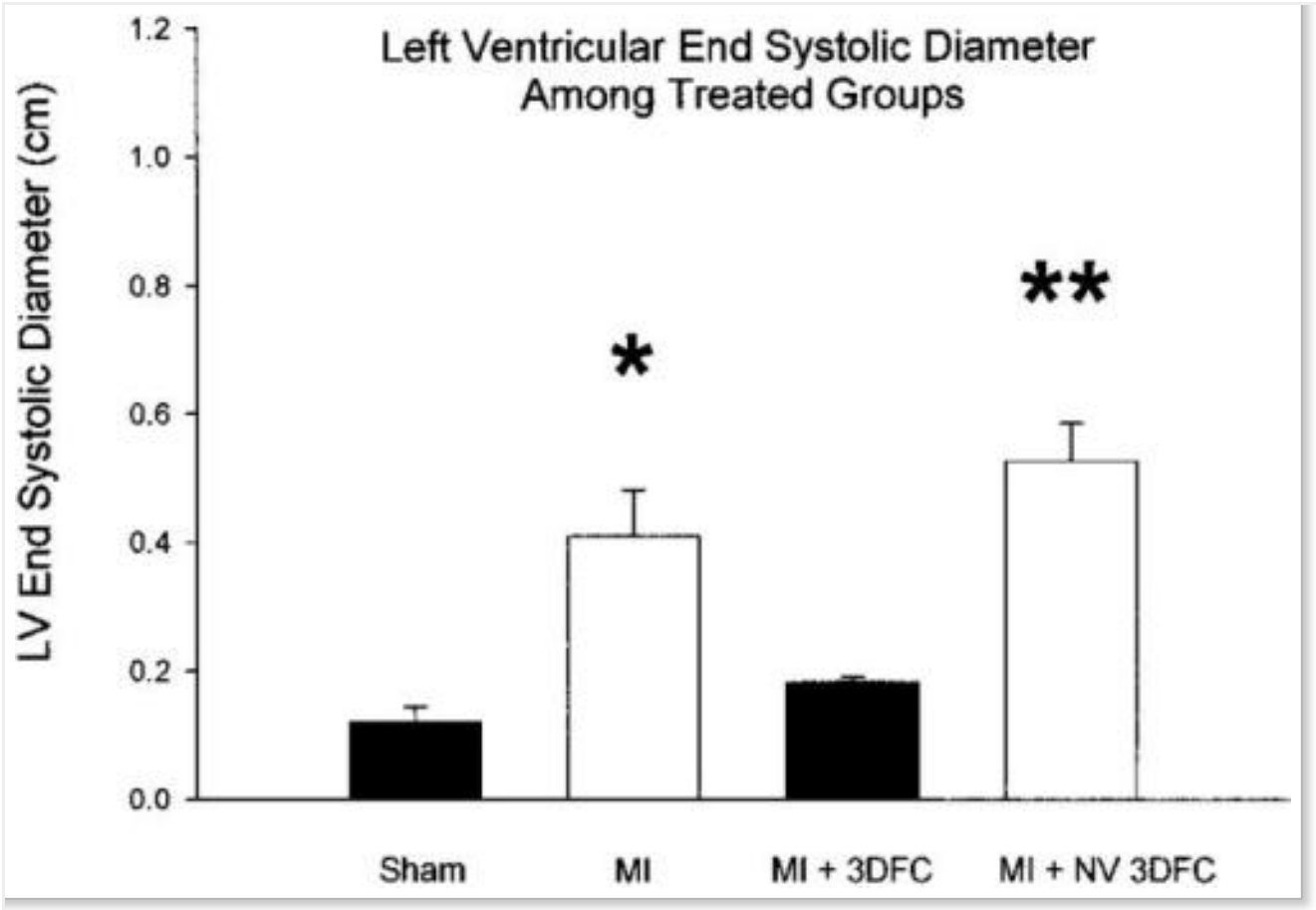


Figure 3.

Echocardiographic measured ejection fraction (EF) in sham, myocardial infarction (MI), MI + 3DFC, MI + 3DFC/Cap (captopril), and MI + 3DFC/NV (nonviable). Note that the viable 3DFC increased the EF. The EF remained increased with the addition of captopril to the viable 3DFC; the nonviable 3DFC did not improve EF. Values are mean ± SE. Sham ($N = 5$); MI ($N = 8$); MI + 3DFC/cap ($N = 10$); MI + 3DFC ($N = 14$); MI + 3DFC (nonviable) ($N = 5$). *$p < 0.05$ sham versus all groups; **$p < 0.05$ MI and MI + 3DFC/NV versus MI + 3DFC/cap and MI + 3DFC.

Figure 4.

Echocardiographic measured systolic displacement of the infarcted anterior wall in sham, myocardial infarction (MI), and MI + 3DFC. Note that the 3DFC improved EF back toward the normal value. Values are mean ± SE. Sham ($N = 6$); MI ($N = 12$); MI + 3DFC ($N = 15$); MI + NV 3DFC ($N = 12$). *$p < 0.05$ versus MI; **$p < 0.05$ versus MI.



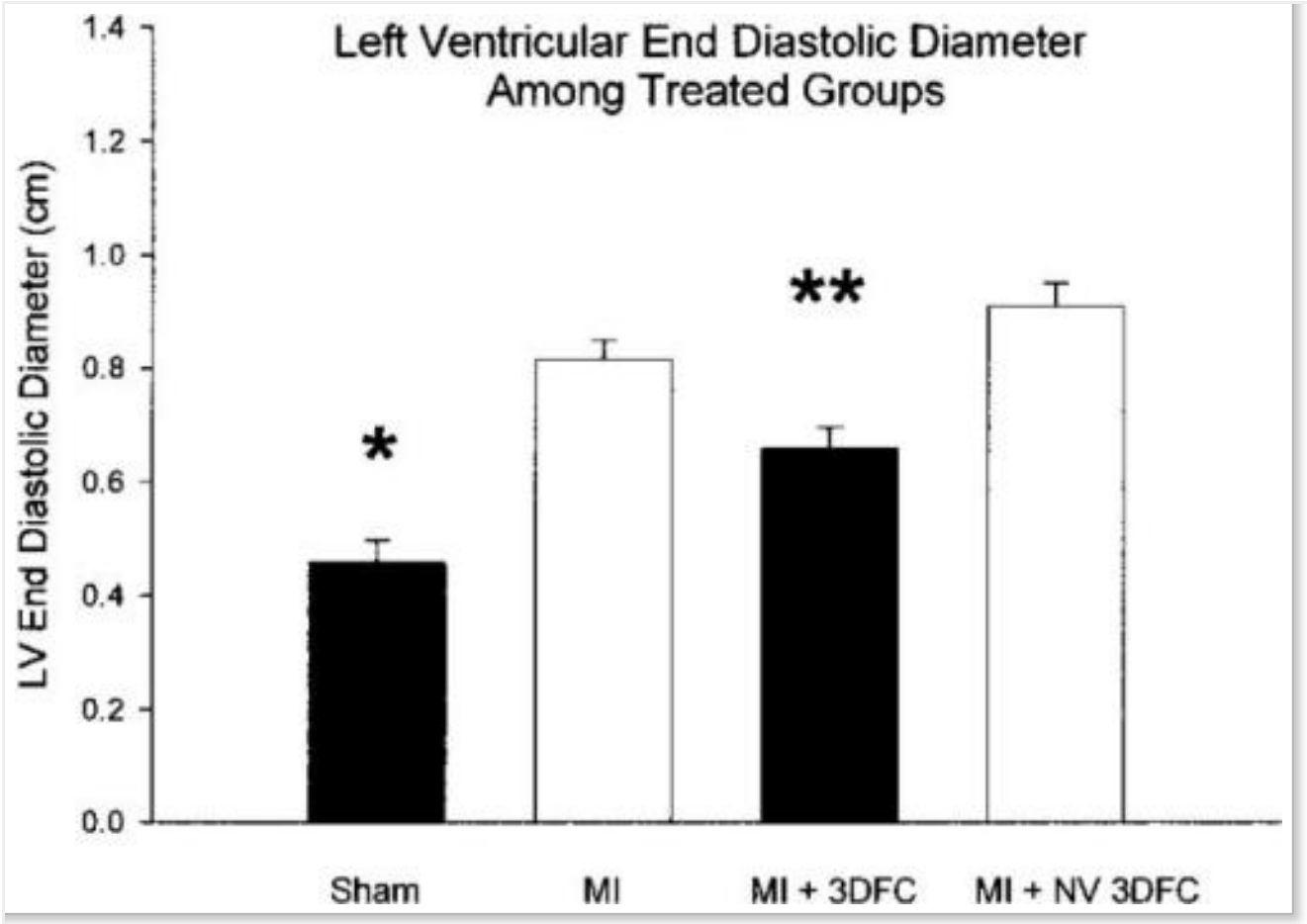


Figure 5.

Echocardiographic measured LV end-diastolic and end-systolic diameters in sham, myocardial infarction (MI), and MI + 3DFC. Note that both the LV end-diastolic diameter and end-systolic diameters decrease with the 3 DFC. Values are mean ± SE. Sham (N=6); MI (N=12); MI + 3DFC (N=15); MI + NV 3DFC, (N=12). *$p < 0.05$ versus sham; **$p < 0.05$ versus MI.

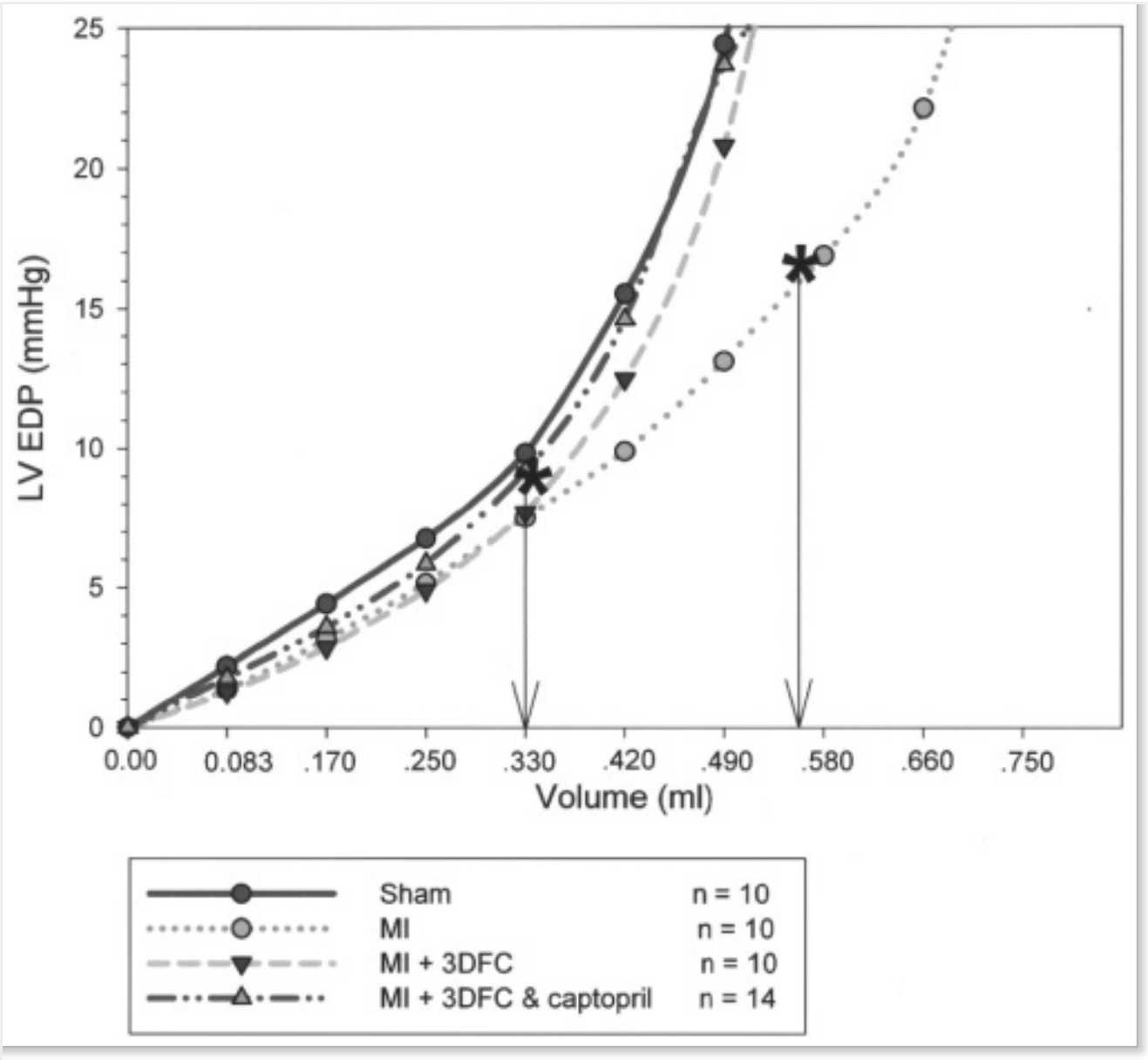


Figure 6.

Pressure–volume (PV) loops in sham, myocardial infarction (MI), MI + 3DFC, and MI + 3DFC/captopril. Note that the major shift in the PV loop was with the addition of captopril where the operating LV end-diastolic volume decreased.

Figure 7.

Anterior wall myocardial blood flow in sham ($N = 11$), at the time of acute myocardial infarction (MI, $N = 7$), MI at 3 weeks ($N = 4$), and MI at 3 weeks with 3DFC ($N = 4$). Note that the 3DFC improved blood flow in the infarcted wall. Values are mean ± SE; $^{*}p < 0.05$ versus baseline and MI (3w) + 3DFC.

Figure 8

Vessel density defined by Factor VIII staining. Note the increase in vessel density in the area with the 3DFC compared to the untreated myocardial infarction (MI). MI ($N = 9$), MI + 3DFC ($N = 8$). Values are mean ± SE. $^{*}p < 0.05$ versus MI.

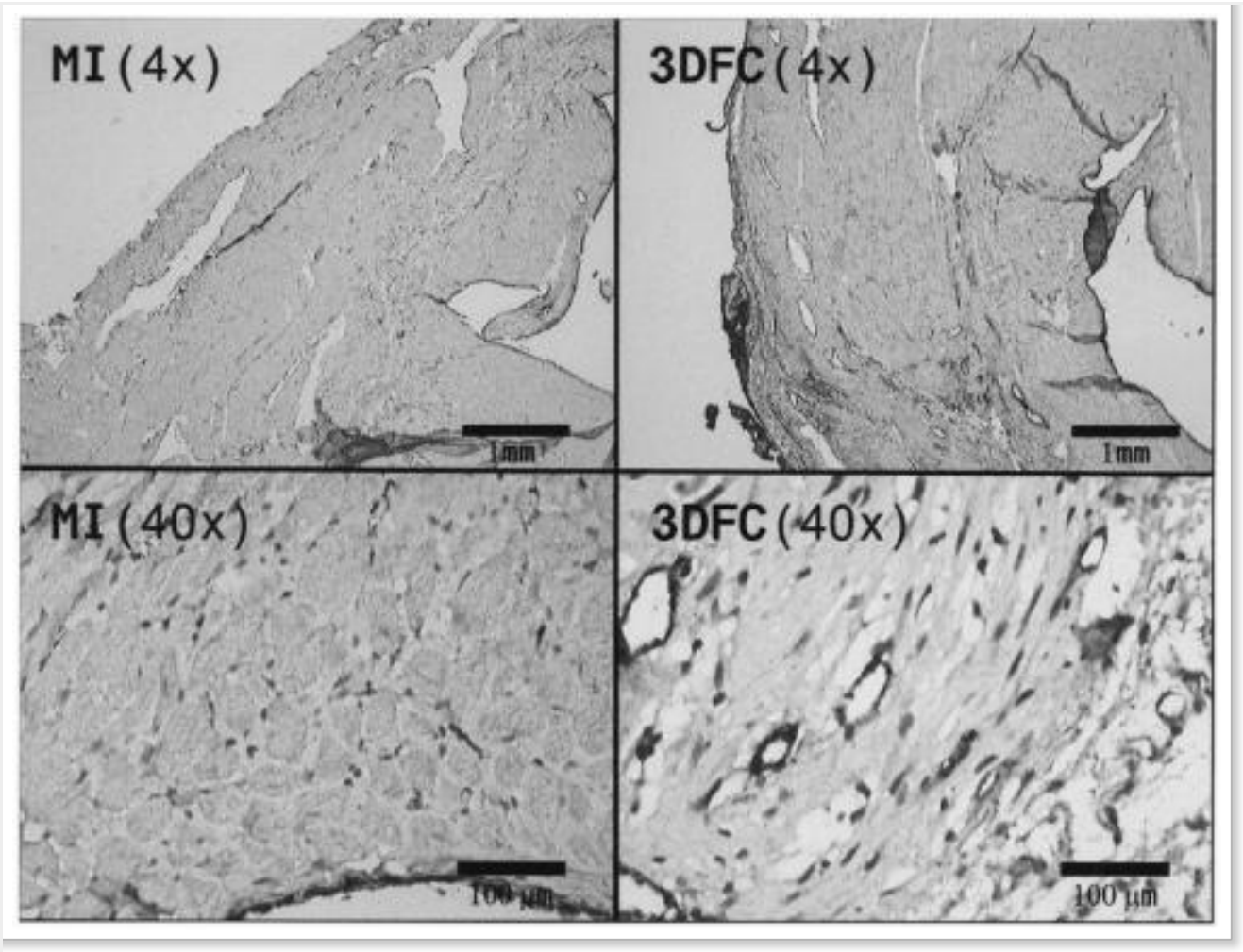


Figure 9.

Histopathology sections of Factor VIII staining in MI + 3DFC (A–C) and MI alone (4× and 40×). Note the increased in Factor VIII staining and vessel density with the 3DFC.

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Echocardiogram Quantification: Quest for Reproducibility and Dependability

Posted in Medical Imaging Technology, Image Processing/Computing, MRI, CT, Nuclear Medicine, Ultra Sound, tagged American Heart Association, Cardiology, Echocardiography, Philips, Reproducibility, VisualSonics on October 12, 2013| 1 Comment »

1 Vote

Echocardiogram Quantification: Quest for Reproducibility and Dependability

Reporter: Aviva Lev-Ari, PhD, RN

How can echo quantification become more reproducible and dependable?

Ivan Salgo **Senior Director, Global Cardiology at**

Innovations in Cardiology

a subgroup of Innovations In Health on LinkedIn.com

Echocardiography encompasses an array of clinically important tasks including quantifying cardiac chamber size, ventricular mass and function.

Based on your experience, how can echo quantification become more reproducible and dependable?

Comments made by Group members:

Yoni

Yoni Tirosh

CEO at M.I. Medical Incentive Ltd.

Hello Ivan,
I've sent you a personal message regarding an innovative development related to Echo use.

Tim

Tim Zepick

Office Manager; Technical Director, Ultrasound at Line Medical

It's impossible.

There are large variations in quality of ultrasound systems. There are also large variations in skill levels of operators. And those skill levels change over time. But the most detrimental factor is that the human body is a dynamic and unique system. Some subjects are technically difficult and LV function is basically impossible to assess, even with an excellent US system. Measurement of LVPWiD is a guess on these patients. Then there are subjects on whom you can obtain excellent images at intercostal space #2, #3, and #4. And the anatomy is bisected at a different angle and might yield three different measurements at each approach. The same can be said for a lot of the 2-D length measurements. I can probably make your RA five centimeters wide, if I try.

That said, doing about 5,000 studies will get you pretty good at recognizing your limitations, realizing the need to remeasure erroneous data, common failings of ultrasound physics and other sources of error.

Thankfully, inexperienced techs get a good education on spotting and evaluating the "exciting" stuff because these nuanced stuff takes time to develop.

 Wayne

Wayne Peterson

Product Manager

Ivan,
As a former Philips employee, hello. My clinical skills included cardiac ultrasound. In response to your question, a software program with edge resolution enhancement and auto analysis would be amazing. It would remove user variability.

 Tony

Tony Gallagher

Clinical Coordinator of Cardiology and Cardio-Pulmonary Rehabilitation at Floyd Medical Center

I agree with Tim that it is not possible. In deference to Wayne; edge recognition software would help. But the variety of equipment skill levels, even peoples varied vision; prevent 100% agreement.

Even at the larger conferences, when you attend the “read with the experts” courses, you see that they tend to disagree looking at the same images.

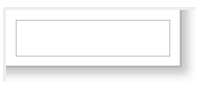
unless equipment, education, and criteria for performing studies gets standardized; not going to happen.

 Alberto

Alberto Gomez

Research Assistant at King’s College London

Reproducibility and reduction (I.e. not complete removal) of variability could be achieved in several ways. For example, to cite a few: multi view imaging to remove view dependency on edge definition and occlusion; angle independent flow quantification using 3D color Doppler; image fusion and compounding with tracked probes; simultaneous (or quasi-simultaneous) multi-prove systems. All these are engineering and research challenges but we will get to them. How long it will take highly depends on how willing manufacturers are to open up to research institutions and how willing research institutions are to share and exploit results.



Aviva Lev-Ari, PhD, RN

Cardiovascular Original Research: Curation Methodology Designer at Leaders in

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http://pharmaceuticalintelligence.com

On right hand side Categories, pl. Click on Medical Imaging
search box
Type
Justin Pearlman, MD, PhD, FACC

Thank you
Aviva Lev-Ari, PhD, RN

 Clifford

Clifford Thornton

Echocardiography Technician at CapitalHealth

You're a very brave man Ivan, asking the holy grail question of echocardiography! I've been doing echoes at prominent institutions for 10 years, been registered in echo since 2006, have performed probably more than 6,000 adult echoes, teach echo to technicians and sometimes residents, attended echo related conferences and read the latest Dr. Feigenbaum and Dr. Otto textbooks – so I can speak to this topic.

Here's the deal. From what I understand, the best echo has to offer as far as EF quantification (which I think is usually the focus) is 3D volume quantification. The problem is, is that primarily due to reimbursement issues this technology has had very slow adoption and application and therefore low availability. A great application of this technology would be evaluating a patient for possible LVAD placement/treatment or heart transplant.

Given this, what most technicians are left with is 2 Dimensional echo. There are many ways we can measure Ejection Fraction with 2D Echo and they include direct 2D measurement (measuring the left ventricular internal dimension at end-diastole (LVIDd) and the left ventricular internal dimension at end-systole (LVIDs). Most modern echo systems have very specific packages that enable fairly easy measurements of these aspects of the heart and are clearly labeled. A technician can also make a similar measurement using M-Mode. The achilles-heel of M-Mode based measurement of EF is that the picture or the heart in the picture (from the parasternal long-axis window/view – PLAX) must be on-axis. If the picture is off-axis, your direct 2D measurements should be more accurate. Side note: this all goes out the window with a poorly trained or lazy echo tech who has little to no idea of what they're doing – and unfortunately there's too many of these out there (read more on this later). So, as far as 2D left ventricular dimension measurements of EF go, direct 2D (on screen) measurements are preferable.

According to a Wake Forest Cardiology conference which I attended several years ago in Orlando, "The Beat Goes On" the best or most accurate measurement of EF with 2D echo (assuming there's a good, well-trained, knowledgeable and hard working echo tech performing the test) is with Simpson's Bi-plane method/Quantification. This measurement is based on

volume of blood in the heart at end-diastole and end-systole (see the pattern). Once this is calculated a technician can then calculate the stroke volume (which most packages calculate automatically once the proper measurements are calculated and entered) and the cardiac output (Stroke volume (SV) X heart rate (HR)). As a reference the heart wants to push around 5 liters of blood per minute to sustain life and normal body function. Of course this can greatly increase with exercise or decrease slightly with rest as can your respiratory function.

The way the Biplane Simpsons' method is performed is that a technician calculates the following from both the apical-4-chamber view and the apical-2-chamber view (again most modern systems have these measurements built into the package and labeled and they can also be exported directly to the preliminary report through DICOM specs.):
1. Left ventricular volume at End-Diastole (LVVED) – A4C

1. Left ventricular volume at End-Systole (LVVES) – A4C

1. Left ventricular volume at End-Diastole (LVVED) – A2C

1. Left ventricular volume at End-Systole (LVVED) – A2C

Yes, you can imagine this is very time consuming. It can be done later once the scan is done however once the patient leaves, you can not go back and adjust your view if you think your picture is foreshortened or off-axis, etc.

Please see very relevant document to this topic from the American Society of Echocardiography, Committee Recommendations:
http://files.asecho.org/files/ChamberQuantification.pdf

 Clifford

Clifford Thornton

Echocardiography Technician at CapitalHealth

cont'd–
The bottom line is that quantification in echo, particularly in calculating EF depends on the situation. Simpsons' method is not performed routinely in most labs because if the EF visually looks normal (around 55% – 70%) from the long-axis, short-axis and apical 4 chamber and apical 2 chamber views then there's usually not a huge need for it; little additional benefit. I try to do it as much as possible because I like to do as best an echo I can and also it's good to practice and a little fun when you have very clear/great quality pictures (ironically these are the people who you know their EF is probably normal the minute they walk through your door!).

There are many tools and techniques one can employ to optimize their 2D/Simpsons' EF measurements. Here are a few:
* the patient into the proper position (left lateral decubitus) — I use a wedge to keep them on their left side and keep their head well supported with a rolled up pillow or rolled up blankets

* the proper echo settings/frequency. Use penetration setting if you have to, but if they have good pictures, use the best resolution setting you can without sacrificing endocardial border definition — otherwise you're defeating the purpose

* the proper breathing techniques (I find from parasternal window it's best to have the patient inhale, exhale all the way and then hold their breath for loop acquisition and best to have them inhale and hold for apical acquisitions – but just play around with it until you get the picture you want).

* the picture on axis and avoid foreshortening — this is very key for the Simpsons' method of discs

Now, you've tried all this, you're sweating, your hand and shoulder are about to fall off, you see stars or angels or both and the patient and their family think you are completely clueless and think you're torturing their Wife/Husband/Daughter/Friend/etc. and you're wondering if you'll have a job tomorrow. So what do you do?

Definity Echo contrast (Perflutren Lipid Microsphere) – http://www.definityimaging.com/ – you say? Yes, possibly. You need to A. Get the patient's consent (although this is beginning to change) B. Establish IV access for the injection of the Definity solution C. Activate the Definity and use it within a certain period D. Utilize it correctly.

Basically Definity contrast is little gas bubbles that reflect the ultrasound beams (for which 2D pictures are generated from pulsed-wave doppler) very well or strongly and allow for a stronger, clearer/better resolution image. The heart walls/endocardial borders are one color and the contrast is the other (the contrast is usually the white-milky substance you see inside the left ventricle while it's filling and contracting. Most people think it's pretty "cool" when they see it and it can make a dramatic difference in how you visually estimate or calculate the EF. As I mentioned, Simpsons' method (the preferred 2D EF calc. method) is highly dependent on operator skill and effort and hence picture quality. And Definity contrast can greatly enhance the picture quality. Last week I had a patient where you could barely see any endocardial border without Definity and visually estimating his EF would be a total shot in the dark. Well, we administered Definity, and I'm not lying it was still a tough scan, but once the Definity was injected and began to appear in the right ventricle and then left, I could see immediately that his EF was completely normal (55-60%). This was important to assess clinically because the patient was in the CCU at the time and he was s/p CABG. Judging whether the EF is normal or not can have a big play in clinical decision making for other conditions.

Ironically getting an accurate EF has to do more with having the right technician perform your test than it has to do with technology or anything else. And unfortunately there's no lack of pitfalls there.

Reza

Reza Mehzad, MD, MPH

Mercy Heart Institute

Full automation for 3D echocardiography volume assessment AND having a safe contrast agents to be used with all echo studies.

Clifford Thornton likes this

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State of Cardiology on Wall Stress, Ventricular Workload and Myocardial Contractile Reserve: Aspects of Translational Medicine

Posted in Electrophysiology, Frontiers in Cardiology and Cardiovascular Disorders, Origins of Cardiovascular Disease, tagged Aviva Lev-Ari, Cardiology, Clinical and Translational Science Award, Justin Pearlman, Left ventricle, Medical research, National Institutes of Health, research, Translational Medicine on September 30, 2013| 4 Comments »

1 Vote

State of Cardiology on Wall Stress, Ventricular Workload and Myocardial Contractile Reserve: Aspects of Translational Medicine (TM)

Author, and Content Consultant to e-SERIES A: Cardiovascular Diseases: Justin Pearlman, MD, PhD, FACC

and

Article Curator, Aviva Lev-Ari, PhD, RN

This article is **based on and all citations are from** the following two articles that have appeared in Journal of Translational Medicine in 2013

#1:

Identifying translational science within the triangle of biomedicine

http://www.translational-medicine.com/content/11/1/126

Griffin M Weber

Journal of Translational Medicine 2013, 11:126 (24 May 2013)

#2:

Integrated wall stress: a new methodological approach to assess ventricular workload and myocardial contractile reserve

http://www.translational-medicine.com/content/11/1/183

Dong H, Mosca H, Gao E, Akins RE, Gidding SS and Tsuda T

Journal of Translational Medicine 2013, 11:183 (7 August 2013)

In this article we expose the e-Reader to

A. The State of Cardiology on

- wall stress
- ventricular workload and
- myocardial contractile reserve

B. Innovations in a Case Study in Cardiology Physiological Research on above subjects

C. Prevailing Models in Translational Medicine

D. Mapping of One Case Study in Cardiology Physiological Research onto Weber's Triangle of Biomedicine.

The mapping facilitate e-Reader's effort to capture the complexity of aspects of Translational Medicine and visualization of the distance on this Triangle between where the results of this case study are and the Human Corner — the Roadmap of the "bench-to-bedside" research, or the "translation" of physiological and basic science research into practical clinical applications.

This article has the following sections:

Introduction

Author: Justin Pearlman, MD, PhD, FACC

Translational medicine aims to fast track the pathway from scientific discovery to clinical applications and assessment of benefits. Cardiovascular examples include novel biomarkers of disease, new heart assist devices, new technologies for catheter intervention, and new medications. The Institute of Medicine's Clinical Research Roundtable describes translation medicine in two fundamental blocks: "…the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention [with] first testing in humans…", and "…the translation of results from clinical studies into everyday clinical practice and health decision making…" [2].

Identifying where contributions are achieving translation has been addressed by the biometric tool called the triangle of biomedine [3].

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This article has the following EIGHT Sections:

I. Key Explanation Models for the Translational Process in BioMedicine, aka Translational Medicine (TM)

II. TM Model selection in this article, for mapping the fit of a Case Study in Cardiology Physiological Research, within the TM Model selected

III. Limitations of the TM Model to explain the Translational Process in BioMedicine

IV. Mapping the fit of a Case Study in Cardiology Physiological Research, within the TM Model selected

V. Clinical Implications of the Case Study in Cardiology Physiological Research

VI. Limitations of the Case Study in Cardiology Physiological Research

VII. The State of Cardiology on

- wall stress
- ventricular workload and
- myocardial contractile reserve

VIII. What are the Innovations of the Case Study in Cardiology Physiological Research

I. Key Explanation Models for the Translational Process in BioMedicine, aka Translational Medicine (TM)

The National Institutes of Health (NIH) Roadmap places special emphasis on "bench-to-bedside" research, or the "translation" of basic science research into practical clinical applications. The Clinical and Translational Science Awards (CTSA) Consortium is one example of the large investments being made to develop a national infrastructure to support translational science, which involves reducing regulatory burdens, launching new educational initiatives, and forming partnerships between academia and industry. However, while numerous definitions have been suggested for translational science, including the qualitative T1-T4 classification, **a consensus has not yet been reached. This makes it challenging to measure the impact of these major policy changes.**

BASIC DISCOVERY -T1-> CLINICAL INSIGHTS -T2-> IMPLICATIONS FOR PRACTICE -T3-> IMPLICATIONS FOR POPULATION HEALTH -T4-> IMPLICATIONS FOR GLOBAL HEALTH

Model A: QUALTITATIVE T1-T4 CLASSIFICATION [(7) & (8-10) in Weber's list of Reference, below]

In biomedicine, **translational science is research that has gone from "bench" to "bedside", resulting in applications such as drug discovery that can benefit human health** [1–6]. However, this is an imprecise description. Numerous definitions have been suggested, including the qualitative T1-T4 classification [7].

Several bibliometric techniques have been developed to quantitatively place publications in the translational spectrum. Narin assigned journals to fields, and then grouped these fields into either "Basic Research" or "Clinical Medicine" [8-10]. **Narin also developed another classification called research levels, in which journals are assigned to "Clinical Observation" (Level 1), "Clinical Mix" (Level 2), "Clinical Investigation" (Level 3), or "Basic Research" (Level 4) [8]. He combines Levels 1 and 2 into "Clinical Medicine" and Levels 3 and 4 to "Biomedical Research".**

Model B: Average research level of a collection of articles as the mean of the research levels of those articles

Lewison developed methods to score the translational research level of individual articles from keywords within the articles' titles and addresses. He defines the average research level of a collection of articles as the mean of the research levels of those articles [11–13] . For validity, one must assume that the keywords reflect content fairly and without bias. If the government adapts such a scoring system to influence funding in order to promote translational research, that will create a bias.

Model C: "Translatability" of drug development projects

A multidimensional scoring system has been developed to assess the "translatability" of drug development projects [29,30]. This requires manual review of the literature which poses difficulties for scalability and consistency across reviewers and over time.

Model D: Fontelo's 59 words and phrases suggesting that the article is Translational

Fontelo identified 59 words and phrases, which when present in the titles or abstracts of articles, suggest that the article is translational [31]. It is an interesting sampling method, but it may present a bias to particular styles of presentation.

Model E: The triangle of biomedicine by Griffin M Weber – This Model is the main focus of

this article

http://www.translational-medicine.com/content/11/1/126

Methods

The Triangle of Biomedicine uses a bibliometric approach to map PubMed articles onto a graph. The corners of the triangle represent research related to animals, to cells and molecules. The position of a publication on the graph is based on its topics, as determined by its Medical Subject Headings (MeSH). Translation is defined as movement of a collection of articles, or the articles that cite those articles, towards the human corner.

Results

The Triangle of Biomedicine provides a quantitative way of determining if an individual scientist, research organization, funding agency, or scientific field is producing results that are relevant to clinical medicine. Validation of the method examined examples that have been previously described in the literature, comparing it to other methods of measuring translational science.

Conclusions

The Triangle of Biomedicine is a novel way to identify translational science and track changes over time. This is important to policy makers in evaluating the impact of the large investments being made to accelerate translation. The Triangle of Biomedicine also provides a simple visual way of depicting this impact, which can be far more powerful than numbers alone. As with any metric, its limitations and potential biases should always be kept in mind. As a result, it should be used to supplement rather than replace alternative methods of measuring or defining translational science. What is unique, though, to the Triangle of Biomedicine, is its simple visual way of depicting translation, which can be far more powerful to policy makers than numbers alone.

Keywords:

Translational science; Bibliometric analysis; Medical subject headings; Data visualization; Citation analysis

II. TM Model selection in this article, for mapping the fit of a Case Study in Cardiology Physiological Research, within the TM Model selected

Model E: The triangle of biomedicine by Griffin M Weber

In this study, we analyze the 20 million publications in the National Library of Medicine's PubMed database by extending these bibliometric approaches in three ways: (1) We divide basic science into two subcategories, research done on animals or other complex organisms and research done on the cellular or molecular level. We believe it is important to make this distinction due to the rapid increase in "-omics" research and related fields in recent years. (2) We classify articles using their Medical Subject Headings (MeSH), which are assigned based on the content of the articles. Journal fields, title keywords, and addresses only approximate an article's content. (3) We map the classification scheme onto a graphical diagram, which we call

the Triangle of Biomedicine, which makes it possible to visualize patterns and identify trends over time.

Article classification technique

Using a simple algorithm based on an article's MeSH descriptors, we determined whether each article in PubMed contained research related to three broad topic areas—animals and other complex organisms (A), cells and molecules (C), or humans (H). An article can have more than one topic area. Articles about both animals and cells are classified as AC, articles about both animals and humans are AH, articles about cells and humans are CH, and articles about all three are ACH. Articles that have none of these topic areas are unclassified by this method.

In order to identify translational research, we constructed a trilinear graph [21], where the three topic areas are placed at the corners of an equilateral triangle, with A on the lower-left, C on the top, and H on the lower-right. The midpoints of the edges correspond to AC, AH, and CH articles, and the center of the triangle corresponds to ACH articles.

An article can be plotted on the Triangle of Biomedicine according to the MeSH descriptors that have been assigned to it. For example, if only human descriptors, and no animal or cell descriptors have been assigned to an article, then it is classified as an H article and placed at the H corner. An article with both animal and cell descriptors, and no human descriptors, is classified as an AC article and placed at the AC point. A collection of articles is represented by the average position of its articles. Although an individual article can only be mapped to one of seven points, a collection of articles can be plotted anywhere in the triangle.

An imaginary line, the Translational Axis, can be drawn from the AC point to the H corner. The position of one or more articles when projected onto this axis is the Translational Index (TI). By distorting the Triangle of Biomedicine by bringing the A and C corners together at the AC point, the entire triangle can be collapsed down along the Translational Axis to the more traditional depiction of translational science being a linear path from basic to clinical research. In other words, the Triangle of Biomedicine does not replace the traditional linear view, but rather provides additional clarity into the path research takes towards translation.

Summary of categories

Mapping A-C-H categories to Narin's basic-clinical classification scheme

The National Library of Medicine (NLM) classifies journals into different disciplines, such as microbiology, pharmacology, or neurology, with the use of Broad Journal Headings. We used Narin's mappings to group these disciplines into basic research or clinical medicine. Individual articles were given a "basic research" score of 1 if they were in a basic research journal and 0 if they were in a "clinical medicine" journal. For each A-C-H category, a weighted average of its articles' scores was calculated, with the weights being the inverse of the total number of basic research (4,316,495) and clinical medicine (11,689,341) articles in PubMed. That gives a numeric value for the fraction of articles within a category that are basic research, which is corrected for the fact that PubMed as a whole has a greater number of clinical medicine articles.

Mapping A-C-H categories to Narin's four-level classification scheme

For each of his four research levels, Narin selected a prototype journal to conduct his analyses: *The Journal of the American Medical Association* (*JAMA*, Level 1), *The New England*

Journal of Medicine (*NEJM*, Level 2), *The Journal of Clinical Investigation* (*JCI*, Level 3), and *The Journal of Biological Chemistry* (*JBC*, Level 4). Each is widely considered a leading journal and has over 25,000 articles spanning more than 50 years. For each A-C-H category, we determined the number of articles from each of these four journals and calculated a weighted average of their research levels, with the weights being the inverse of the total number of articles each journal has in PubMed.

III. Limitations of the TM Model to explain the Translational Process in BioMedicine: The triangle of biomedicine by Griffin M Weber

This work is limited in several ways. It takes at least a year for most articles to be assigned MeSH descriptors. During that time the articles cannot be classified using the method described in this paper. Also, our classification method is based on a somewhat arbitrary set of MeSH descriptors—different descriptors could have been used to map articles to A-C-H categories. However, the ones we used seemed intuitive and they produced results that were consistent with Narin's classification schemes. Finally, any metric based on citation analysis is dependent on the particular citation database used, and there are significant differences among the leading databases [22]. In this study, we used citations in PubMed that are derived from PubMed Central because they are freely available in their entirety, and therefore our method can be used without subscriptions to commercial citation databases, such as Scopus and Web of Science, which are cost-prohibitive to most people. However, because these commercial databases have a greater number of citations and index different journals than PubMed, they might show shorter or alternative paths towards translation (i.e., fewer citation generations or less time). Though, as described in our Methods, there is evidence that suggests these differences might be relatively small. Selecting the best citation database for identifying translational research is a topic for future research.

Another area of future research could attempt to identify a subset of H articles that truly reflect changes in health practice and create a separate category P for these articles. This might be possible, for example, by using Khoury's approach of using PubMed's "publication type" categorization of each article to select for those that are clinical trials or practice guidelines [7]. This could be visualized in the Triangle of Biomedicine by moving H articles to the center of the triangle and placing P articles in the lower-right corner, thereby highlighting research that has translated beyond H into health practice.

IV. Mapping the fit of a Case Study in Cardiology Physiological Research, within the TM Model selected

The triangle of biomedicine by Griffin M Weber

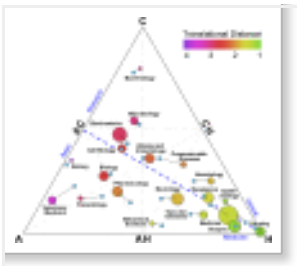

Figure 1. Disciplines mapped onto the Triangle of Biomedicine. The corners of the triangle

correspond to animal (**A**), cellular or molecular (**C**), and human (**H**) research. The dashed blue line indicates the Translational Axis from basic research to clinical medicine. The position of each circle represents the average location of the articles in a discipline. The size of the circle is proportional to the number of articles in that discipline. The color of the circle indicates the Translational Distance (TD)—the average number of citation generations needed to reach an H article. The position of the light blue box connected to each discipline represents the average location of articles citing publications in that discipline. To provide clarity, not all disciplines are shown. Note however, that if authors knew this measurement would be applied and could affect their funding, then they might increase human study citation of basic research to game the "translational distance."

For this article we selected **A Case Study in Cardiology Physiological Research**

Integrated wall stress: a new methodological approach to assess ventricular workload and myocardial contractile reserve

Hailong Dong[124], **Heather Mosca**[1], **Erhe Gao**[3], **Robert E Akins**[1], **Samuel S Gidding**[2] and **Takeshi Tsuda**[12*]

This study appeared in 2013 in the Journal of Translational Medicine. It studied mice, creating heart attacks in order to evaluate the physiologic significance of "integrated wall stress" (IWS) as a marker of total ventricular workload. The measure IWS was obtained by integrating continuous wall stress curve by accumulating wall stress values at millisecond sampling intervals over one minute, in order to include in wall stress effects of heart rate and contractility (inotropic status of the myocardium). As an example of translational medicine, it raises numerous issues. As a mouse study, it qualifies as basic science. It examines the impact of heart attack on changes inducible by the inotropic agent dobutamine. If the concept were to influence clinical care and outcomes, it would qualify as translational. All of the tools applied to the mice are applicable to patients: heart attacks (albeit not purposefully induced), the echocardiography measurements, and the dobutamine impact. That enables citation of human studies in the references, and ready application to human studies in the future. Mice however have much faster heart rates, so the choice of one minute for the integral may have different significance for humans. Gene expression was also measured. The authors conclude IWS represents a balance between external ventricular workload and intrinsic myocardial contractile reserve. The fact that the Journal has the word "translational" may represent a bias. Many of the links between animal and human focused references occur electively in the discussion section. The authors propose the measurement might help identify pre-clinical borderline failing of contractility. If so, the full axis of translational value will require that IWS can improve outcomes. Currently, blood levels of brain naturetic peptide are used as a marker of myocardial strain that may help identify early failing contractility. Presumably, early recognition could identify a population that might benefit from early intervention to forestall progression. Evidence based medicine will have difficulties. First, it is biased by the "Will Roger's Effect" whereby early recognition of a disease subdivides the lowest class, inherently shifting the apparent status of each half of the subdivision (Will Roger's made a joke that when Oklahoma residents moved to California for the gold rush, they improved the average intelligence of both groups, an observation adapted to explain a redefinition bias). Second, the actual basis for a change in clinical application will be complex, with political as well as scientific

influences. Third, it will be even more difficult to discern its impact on outcomes, even if targeted therapy for patients with distinctive IWS is associated with an apparent improvement in outcomes. Convincing documentation would require extensive comparisons and controlled studies, but once a method is clinically adapted, it is commonly considered unethical to perform a controlled study in which the "preferred method" is not applied to a group.

V. Clinical Implications of the Case Study in Cardiology Physiological Research

Background

Wall stress is a useful concept to understand the progression of ventricular remodeling. We measured cumulative LV wall stress throughout the cardiac cycle over unit time and tested whether this "integrated wall stress (IWS)" would provide a reliable marker of total ventricular workload.

Methods and results

We applied IWS to mice after experimental myocardial infarction (MI) and sham-operated mice, both at rest and under dobutamine stimulation. Small infarcts were created so as not to cause subsequent overt hemodynamic decompensation. IWS was calculated over one minute through simultaneous measurement of LV internal diameter and wall thickness by echocardiography and LV pressure by LV catheterization. At rest, the MI group showed concentric LV hypertrophy pattern with preserved LV cavity size, LV systolic function, and IWS comparable with the sham group. Dobutamine stimulation induced a dose-dependent increase in IWS in MI mice, but not in sham mice; MI mice mainly increased heart rate, whereas sham mice increased LV systolic and diastolic function. IWS showed good correlation with a product of peak-systolic wall stress and heart rate. We postulate that this increase in IWS in post–MI mice represents limited myocardial contractile reserve.

Conclusion

We hereby propose that IWS provides a useful estimate of total ventricular workload in the mouse model and that increased IWS indicates limited LV myocardial contractile reserve.

Keywords:

Wall stress; Ventricular workload; Myocardial contractile reserve; Ventricular remodeling

Clinical implications

IWS can be estimated by obtaining IWS index, which is calculated non-invasively by simultaneous M-mode echocardiogram and cuff blood pressure measurement, i.e., PS-WS instead of ES-WS and heart rate. This will provide a sensitive way to detect subclinical borderline failing myocardium in which the decline in LV myocardial contractile reserve precedes apparent LV dysfunction. This method may be clinically useful to address LV myocardial reserve in those patients who are not amenable to perform on exercise stress test, such as immediate post-operative patients under mechanical ventilation, critically ill patients with questionable LV dysfunction, and patients with primary muscular disorders and general muscular weakness (i.e., Duchenne muscular dystrophy).

VI. Limitations of the Case Study in Cardiology Physiological Research

There are certain limitations in this study.

- First, wall stress measurement is reliable when there is an equal wall thickness with symmetrical structure. Obviously, with the creation of small MI, there is an asymmetry of LV myocardium in both structure and consistency (myocardium vs. scar tissue). However, the scar tissue is small and restricted to the LV apex (approximately 14% of entire LV myocardium [5]). In fact, most of LV wall was thickened after induction of this small experimental MI. Nevertheless, we acknowledge that this is our major limitation.
- Secondly, there is an individual variability in response to dobutamine stimulation even in sham mice. Although the average sham mice (n = 5) showed only a modest increase in HR, PS-WS, and IWS during dobutamine stimulation, one mouse presented in Figure 1 showed a notable increase in HR and PS-WS in response to dobutamine. Nevertheless, even with increased HR and PS-WS, the calculated IWS remained relatively unchanged in the sham-operated mice.
- Lastly, the reliability of IWS index is based upon the stipulation that ED-WS is significantly low compared with the systolic wall stress. Thus, IWS index may not be accurate in obvious volume overload cases and/or dilated hearts with LV dysfunction where ED-WS is significantly higher than that in normal condition. Of note, ED-WS in human is higher than that in mice in relation to PS-WS, probably around 15 to 20% of PS-WS [12].

VII. State of Cardiology on

- **wall stress**
- **ventricular workload and**
- **myocardial contractile reserve**

Ventricular remodeling is a chronic progressive pathological process that results in heart failure after myocardial infarction (MI) or persistent unrelieved biomechanical overload [1,2]. Persistent and unrelieved biomechanical overload in combination with activation of inflammatory mediators and neurohormones is thought to be responsible for progressive ventricular remodeling after MI [3,4], but studies to investigate specific mechanisms in animals are hampered by the difficulty involved in quantifying biomechanical workload *in vivo*. The magnitude of ventricular remodeling advances in line with progressive ventricular geometric changes including myocardial hypertrophy and chamber dilatation with accompanying functional deterioration [1,2]. Previously, we proposed that post-ischemic ventricular remodeling is a pathological spectrum ranging from benign myocardial hypertrophy to progressive heart failure in the mouse model in which the prognosis is primarily determined by the magnitude of residual hemodynamic effects [5]. However, there has been no optimum quantitative measurement of ventricular workload as a contributory indicator of ventricular remodeling other than wall stress theory to explain how ventricular dilatation and hypertrophy develop after loss of viable working myocardium [6,7].

The concept of ventricular wall stress was introduced by Strauer et al. as a primary determinant

of myocardial oxygen demand [8]. They indicated that overall myocardial energy demand depends upon intramyocardial wall tension, inotropic state of the myocardium, and heart rate. Wall stress theory is commonly introduced to explain development of concentric hypertrophy in chronic pressure overload and progressive ventricular dilatation in the failing heart. One study argued that peak-systolic wall stress increased as LV function worsened in a chronic volume overloaded status [9], and another suggested that peak-systolic wall stress closely reflected LV functional reserve during exercise [10]. However, **the effect of heart rate or myocardial contractility was not considered in either study. Heart rate has been shown to be one of several important factors contributing to myocardial oxygen consumption [11].**

Herein, we introduce a novel concept of "integrated wall stress (IWS)" to assess its significance as a marker of total ventricular workload and to validate its physiological relevance in the mouse model. The concept of continuous LV wall stress measurement was reported previously, but authors did not address the overall effects of changing wall stress during the cardiac cycle on the working myocardium [12]. We have defined IWS as cumulative wall stress over unit time: IWS was obtained by integrating continuous wall stress curve by accumulating wall stress values at millisecond sampling intervals over 1 min. By calculating IWS, we were able to incorporate the effects of not only systolic wall stress, but also of heart rate and inotropic status of the myocardium. These data were analyzed against conventional hemodynamic parameters in animals with and without MI in conjunction with incremental dobutamine stress. We hypothesize that unchanged IWS represents stable ventricular myocardial contractile reserve and that increase in IWS implies an early sign of mismatch between myocardial reserve and workload imposed on ventricular myocardium.

VIII. What are the Innovations of the Case Study in Cardiology Physiological Research

IWS measures total wall stress throughout the cardiac cycle over a unit time (= 1 min) including the effect of heart rate and inotropic state of the ventricular myocardium, whereas one-spot measurement of PS-WS and ED-WS only reflects maximum and minimum wall stress during a cardiac cycle, respectively. We hypothesized that increase in IWS indicates failure of myocardium to counteract increased ventricular workload. We have measured IWS in the mouse model in various physiological and pathological conditions to validate this hypothesis. Unchanged IWS observed in sham operated mice may imply that the contractile reserve of ventricular myocardium can absorb the increased cardiac output, whereas increased IWS after MI suggests that ventricular workloads exceeds intrinsic myocardial contractile reserve. Thus, we postulate that IWS is a reliable physiological marker in indicating a balance between external ventricular workload and intrinsic myocardial contractile reserve.

#1

IWS and myocardial reserve

"Wall stress theory" is an important concept in understanding the process of cardiac hypertrophy in response to increased hemodynamic loading [16]. When the LV myocardium encounters biomechanical overload, either pressure overload or volume overload, cardiac hypertrophy is naturally induced to normalize the wall stress so that myocardium can minimize the increase in myocardial oxygen demand; myocardial oxygen consumption depends mainly

on systolic wall stress, heart rate, and contractility [8,17]. A question arises whether this hypertrophic response is a compensatory physiological adaptation to stabilize the wall stress or a pathological process leading to ventricular remodeling and heart failure. Physiological hypertrophy as seen in trained athletes reveals increased contractile reserve, whereas pathological hypertrophy shows a decrease in contractile reserve in addition to molecular expression of ventricular remodeling [18–20]. However, what regulates the transition from compensatory adaptation to maladaptive process is not well understood.

Systolic wall stress has been studied extensively as a clinical marker for myocardial reserve. Systolic wall stress reflects the major determinants of the degree of LV hypertrophy and plays a predominant role in LV function and myocardial energy balance [17]. It has been shown that increased systolic wall stress inversely correlates with systolic function and myocardial reserve in patients with chronic volume overload [9,10,21], chronic pressure overload [22,23], and dilated cardiomyopathy [24]. However, one-point measurement of systolic wall stress does not encompass the effect of heart rate and contractile status, the other critical factors that affect myocardial oxygen demand [11]. The idea of IWS has been proposed to incorporate wall stress throughout the cardiac cycle and reflects the effects of heart rate and contractile status.

Myocardial oxygen consumption is determined mainly by ventricular wall stress, heart rate and contractility [17], which are all incorporated in IWS measurement. Continuous measurement of LV wall stress was previously reported in humans [12,15] and dogs [11] with a similar method, but not in mice. By integrating the continuous WS over one minute, we estimated the balance between myocardial contractile reserve and total external ventricular workload and examined its trend in relation to inotropic stimulation in the mouse heart *in vivo*. In this study, we have proposed unchanged IWS as a marker of sufficient myocardial contractile reserve, since increased wall stress demands higher myocardial oxygen consumption. Indeed, systolic wall stress does not increase with strenuous isometric exercise in healthy young athletes [25]. Thus, we propose that increase in IWS indicates diminished myocardial contractile reserve.

#2

Small MI model as a unique model to study early phase of progressive ventricular remodeling

A complex series of protective and damaging events takes place after MI, resulting in increased ventricular workload [26]. Initial ventricular geometric change is considered as a primary compensatory response to counteract an abrupt loss of contractile tissue. In classical theories of wall stress, which rely on the law of Laplace, the mechanisms of progressive ventricular dilatation and functional deterioration of the LV are attributed to the increased wall stress that is not compensated by the intrinsic compensatory mechanisms [2,16]. Although this theory is obvious in advanced stage of heart failure, the subclinical ventricular remodeling following borderline cases such as following small MI with initial full compensatory response is not well explained.

Study shown that our small MI model induced concentric hypertrophy without LV dilatation as if initial myocardial damage was completely compensated (Figure 2) [5]. Although LV hypertrophy is induced initially to normalize the wall stress and to prevent ventricular dilatation, this hypertrophy is not altogether a physiological one because of decreased inotrophic and lusitropic reserve when stimulated with dobutamine (Figure 4) and because of

simultaneous molecular and histological evidence of remodeling in the remote nonischemic LV myocardium (Figure 3). IWS and PS-WS become normalized in small MI at rest under anesthesia as a result of reactive hypertrophy accompanied by increased ANP and BNP mRNA level. Borderline maladaptive LVH is characterized by maintained LV performance at the expense of limited myocardial contractile reserve, and this abnormality can be unmasked by inotropic stimulation [18]. The trend of IWS at rest and with dobutamine stimulation suggests that MI mice were likely exposed to higher IWS during usual awake and active condition than sham-operated mice. In contrast, **systolic wall stress in the pressure overload-induced LV hypertrophy showed a level comparable to that of sham both at rest and under stimulation by 1 adrenergic agonist, prenalterol, with comparable heart rate changes [27]. For this reason, IWS assessment by measuring cumulative WS in a unit time with and without inotropic stimuation should serve as a sensitive marker to assess whether induced LV hypertrophy is a compensatory physiological adaptation process or a pathological maladaptation process. Increased IWS that indicates imposed workload surpassing myocardial contractile reserve is likely to become a major driving factor in inducing progressive ventricular remodeling or initiating deleterious maladaptive processes after MI.**

#3

IWS represents myocardial oxygen demand that can be estimated non-invasively

Study demonstrated a very good correlation between IWS and the product of PS-WS and HR ("IWS index") in both MI and sham-operated hearts (Figure 6). This formula appears physiologically acceptable provided that ED-WS is sufficiently low compared with the PS-WS (approximately 10%, as is shown in Figures 4B and C). **ES-WS was previously introduced as a useful tool for assessing myocardial loading status and myocardial oxygen consumption**, but its measurement requires complicated preparation [28,29]. Because there is an excellent correlation between PS-WS and ES-WS, it has been demonstrated that ES-WS can be substituted by PS-WS [28], which can be easily obtained non-invasively [30]. ES-WS was previously determined as a useful marker to quantify LV afterload and contractility that can be simply and accurately measured non-invasively [15]. As myocardial oxygen consumption is mainly dependent upon systolic wall stress, contractility, and heart rate, it seems reasonable to propose that IWS and IWS index represent the status of myocardial contractile reserve.

Conclusions & Next Phases in Translational Medicine and Cardiology Physiological Research

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Visual and numeric scores that assess the commitment to translation of basic discoveries to measured impact on human outcomes followed by increased prevalence of the benefits is of course desirable, but fraught with challenges. Metrics of translational medicine may lead to rewards that can "game" the system by promoting choices of MeSH codes that augment the score for individual articles and/or clusters of work from a center of research without correlation to the actual impact of the body of work. The fairness of a metric also must account for division of labor whereby one group of researchers achieves major basic discoveries that ferment useful applications to improved outcomes in patient care, while others focus on

applications or application assessments that may have widely disparate degrees of impact on the reduction to practice, validation and dissemination of improved care.

Thus in order to promote useful metrics of translational medicine progress, we propose a set of metrics on the metrics:

1. impact of reviewer skill/bias

2. impact of author coding/bias

3. ability to assess an impact factor independent of author word choices

4. ability to credit basic research for its downstream impact on other researchers culminating in clinical applications, validation, and dissemination of human benefits

5. ability to discern pioneering advances from "me too" duplications of effort and minor variations on work of the same group or others

6. ability to assess cost effectiveness, including the occurrences of subsequent re-investigations to clarify issues that could have been addressed in the instance study

7. ability to compute contribution to quality life year gain per dollar of added care

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Identifying translational science within the triangle of biomedicine

http://www.translational-medicine.com/content/11/1/126

Griffin M Weber

Journal of Translational Medicine 2013, 11:126 (24 May 2013)

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