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HEART RESEARCH

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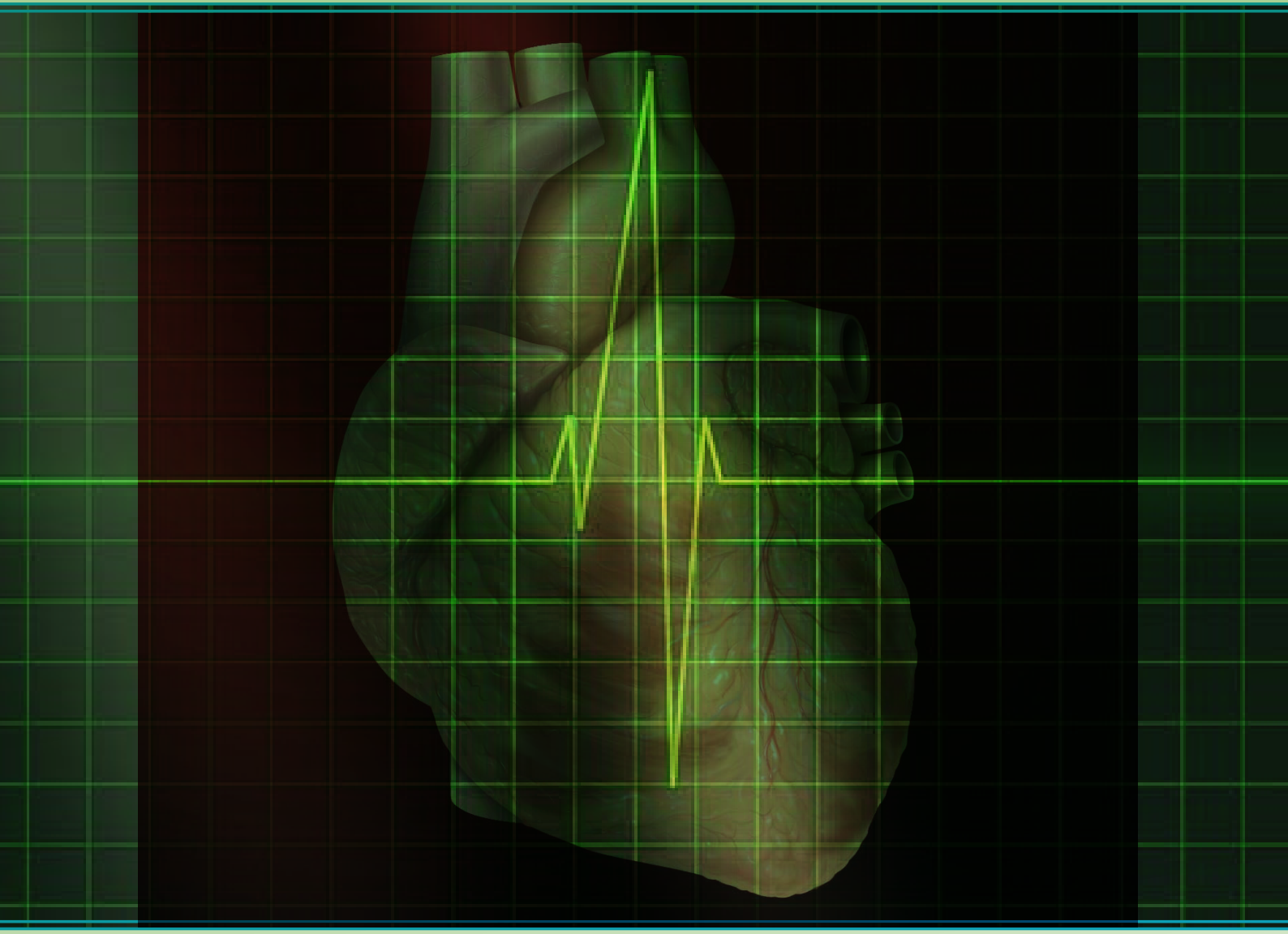

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Editorial

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Shehata M. Nicorandil: what is beyond the anti-anginal action? *Heart Res Open J*. 2015; 2(4): e6-e8.

Nicorandil: What is Beyond the Anti-Anginal Action?

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Incidence of Contrast Induced Nephropathy (CIN) among ischemic heart disease patients subjected to coronary catheterization is highly dependent on the kidney function before contrast media administration and relevant risk factors, of which diabetes mellitus is the most important one.[1] Incidence of CIN ranges from <2% in the general population up to 50% in patients with Advanced Kidney Disease (AKD)[2] and it is the third most common cause of hospital acquired renal failure.[3] Development of contrast media started by the first ionic, high-osmolar contrast agent (sodium acetrizoate) brought by Vernon Wallingford in 1953 and continued till development of the second generation non-ionic media in 1980's.[1] The exact mechanisms underlying CIN are still unclear. However, it was postulated that in addition to their direct toxic effects on renal tubular epithelial cells, contrast media trigger acute renal ischemia by inducing an imbalance between vasodilatory and vasoconstrictive factors.[4] Scientific research for identification of renoprotective agents that can prevent CIN is continuously going on. No pharmacological approach has yet been shown to provide consistent protection. Furosemide, dopamine, atrial natriuretic peptide, sodium bicarbonate, sodium chloride, mannitol, endothelin receptor antagonists, ascorbic acid, fenoldopam, theophylline, N-acetylcysteine, trimetazidine and statins were all previously evaluated in prospective, randomized trials, showing positive or controversial results.[5-7]

Nicorandil is an anti-anginal medication that has the dual properties of a K+ATP channel agonist and a Nitric Oxide (NO) donor.[8] It was reported that activation of the K+ATP channel reduced renal injury (due to ischemia and reperfusion) by preventing accumulation of reactive oxygen radicals. These data suggest that nicorandil may protect the kidney against ischemic injury associated with the use of contrast media by decreasing calcium inflow to the tubular cells, inhibiting the accumulation of reactive oxygen species, suppressing synthesis of endothelin-1, and inducing NO production.[9]

Two prominent studies reported contradicting results concerning feasibility of using Intravenous (IV) nicorandil as a CIN-preventing agent.[10,11] The first one is the PRINCIPLE study (a randomized controlled multicenter study), that was conducted on a total of 166 patients (nicorandil n=81; control n=85) with an estimated glomerular filtration rate <60 mL/min. Nicorandil (12 mg dissolved in 100 mL of 0.9% saline) was administered intravenously for 30 minutes just prior to coronary angiography in the nicorandil group. The same volume of only saline was given to the control group. An iso-osmolar, non-ionic contrast medium, was used. The primary endpoint was the incidence of CIN, defined as >0.5 mg/dL increase or >25% rise in serum creatinine level within 48 hours of contrast exposure compared to baseline. The incidence of CIN did not differ between both groups (6.8% *vs.* 6.6%, p=0.794). It was concluded that prophylactic IV infusion of nicorandil did not decrease the incidence of CIN in patients with renal dysfunction undergoing coronary angiography. Authors assumed that IV nicorandil might be effective when administered at a different dosing regimen. Additionally, the majority (>75%) of the patients included in their study belonged to relatively lower CIN risk groups. percutaneous coronary intervention (PCI) was performed in 38.9% of the patients, and only 24.8% of the included patients required contrast media volume ≥150 mL. These data most probably led to an incidence of CIN that was much lower than what was assumed for the

calculation of the study sample size i.e. underpowered study.[10]

The other study was recently conducted by Nawa, et al.[11] It was a prospective randomized single center trial applying the same definition of CIN. They included 213 patients undergoing elective PCI and with a high serum cystatin C level (greater than 0.95 mg/dL in males and 0.87 mg/dL in females). Patients were randomized in to a saline group (n=107) or a nicorandil group (n=106, 96 mg of nicorandil was dissolved in 100 mL of 0.9% saline then infused in addition to saline for 4h before and 24 h after PCI). A low-osmolar, non-ionic, contrast medium, was used. All patients showed an estimated glomerular filtration rate <60 mL/min. The average percent increases in serum creatinine and cystatin C following PCI were significantly lower in the nicorandil group. The average percent decline in the estimated glomerular filtration rate was lower in the nicorandil group. Accordingly, the incidence of CIN was significantly lower in the nicorandil group (2.0% *vs.* 10.7%, $p<0.02$). Univariate regression analysis revealed nicorandil IV infusion to be the only significant predictor of CIN development. The study still face the limitation of utilizing the uncommonly used indicator of renal dysfunction; cystatin C, in addition to being a single center study.[11]

The main discrepancy between both studies, concerning methodology, can be summarized in two points. The first one is that all patients in the second study underwent PCI, which means a higher mean contrast volume (140 ml *vs.* 125 ml). The second one is related to nicorandil infusion regimen. It is assumed that the detrimental effect of the relatively high contrast volume was negated by more intensive exposure to IV nicorandil in the second study.

The recently published study by Nawa, et al.[11] opens the door for more research work targeting the same subject. Many future perspectives can be addressed, for example; could a more intensive dosing regimen bring more reduction in CIN incidence? Does it worth tackling patients with more severe renal dysfunction? What about using an intensive oral dosing regimen instead of IV infusion? Answers are expected in the near future.

CONFLICTS OF INTEREST

The author has no financial interest in or financial conflict with the subject matter discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Editorial

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Anthracycline Cardiotoxicity: Strategies for Prevention and Intervention

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KEYWORDS: Anthracycline cardiotoxicity; Echocardiography; Strain imaging; Global longitudinal strain.

The cardiotoxic effects of anthracycline compounds, used extensively to treat malignancies such as breast cancer and lymphoma, are well known.[1,2] However, despite efforts towards cardioprotective strategies and early detection of anthracycline cardiotoxicity, defined as decline in Left Ventricular Ejection Fraction (LVEF) of ≥10% from baseline or to <50%,[3,4] there is currently no consensus on the optimal approach. Current clinical practice guidelines recommend serial LVEF monitoring to identify cardiotoxicity in high-risk patients receiving anthracyclines;[3,4] however, it has come to light that LVEF reduction may be a late manifestation of cardiotoxicity,[5,6] with potentially limited prospects for reversibility.[7-9] Recently, echocardiographic strain imaging has emerged as a promising way to detect subclinical cardiotoxicity prior to LVEF reduction,[10-13] where small reduction in Global Longitudinal Strain (GLS) has been identified as a robust predictor of future LVEF reduction and cardiac events.[14-16] The reliability of this approach in patients treated with anthracyclines has been specifically evaluated,[17-19] with reported cardiotoxicity rates ranging from <1% to 32%.[20] Recent studies have established a GLS reduction of ≥11% as a strong predictor of cardiotoxicity.[19,21-24]

Strategies to mitigate anthracycline cardiotoxicity may be classified as pre-emptive (primary prevention) *versus* reactive (secondary prevention).[2] For primary prevention, conventional treatments for heart failure, including beta-blockers and angiotensin antagonists, have been evaluated, with promising results in recent meta-analyses.[25,26] In the recently completed PRADA study, a randomized controlled trial comparing primary prevention of cardiotoxicity with metoprolol, candesartan, *versus* matched placebos in 120 patients treated with anthracyclines with or without trastuzumab for early breast cancer,[27,28] pre-emptive candesartan was shown to result in a statistically significantly attenuation in LVEF decline. In contrast, no similar effect was found with metoprolol succinate use. Additional trials and longer follow-up period are needed to confirm these findings.

Because a primary prevention strategy may needlessly expose many patients to potential adverse effects, secondary prevention strategies are of interest. The implicit assumption of such a strategy is that high risk patients would be detected early enough to be able to initiate treatment while cardiotoxicity is still reversible. In addition to echocardiographic strain, cardiac biomarkers, such as troponin and NT-proBNP, have been evaluated for this purpose. In particular, the degree and duration of troponin elevation was shown to be closely correlated with left ventricular dysfunction[29,30] and in one randomized controlled trial, initiation of enalapril in patients with early troponin leak following chemotherapy was shown to be associated with significant improvement in LVEF at 1 year follow up.[31] However, troponin elevation is not always present even in the setting of echocardiographic findings consistent with cardiotoxicity,[32-35] and thus, echocardiographic strain imaging may be a more reliable indicator for secondary prevention.

In a recent prospective observational study involving a secondary cardioprotective strategy based on strain imaging,[21] Negishi, et al. evaluated changes in strain parameters in patients undergoing treatment with anthracyclines and/or trastuzumab, where those showing ≥11% drop in GLS at 6 months were followed for an additional 6 months with or without initiation of beta blocker therapy. In the treatment group, GLS and LVEF were significantly improved at 12 months, with significant association with beta-blocker therapy in multivariable analysis. While preliminary in nature, this study is significant for being the first to utilize strain imaging in guiding initiation of cardioprotective therapy.

In conclusion, both primary and secondary cardioprotective strategies with beta-blockers and angiotensin antagonist therapy for anthracycline cardiotoxicity hold promise at this time. In adopting a secondary prevention strategy, GLS measured by echocardiographic strain imaging may be a useful and reliable indicator for timing of intervention. Additional randomized controlled trials with long term follow-up are needed in order to determine the best strategies for prevention of anthracycline cardiotoxicity.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Illustration

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An Educational and Illustrative Case Report of Late Complications Following Repair of Tetrology of Fallot

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ABBREVIATIONS: TOF: Tetralogy of Fallot; RVOT: Right Ventricular Outflow Tract; LV: Left Ventricle; RV: Right Ventricle; IAS: Interatrial septum; IVS: Interventricular septum; PV: Pulmonary Valve; PR: Pulmonary Regurgitation; PA: Pulmonary Artery; PI: Pulmonary Inflow (on Doppler); LA: Left Atrium; RA: Right Atrium.

Severe Pulmonary Regurgitation (PR) and its impact on the Right Ventricle (RV) are recognized late complications of repaired cases of Tetralogy of Fallot (TOF). Relief of Right Ventricular Outflow Tract (RVOT) obstruction by transannular patching or infundibulectomy resulted in obligate pulmonary regurgitation in early surgical era. We present classic echocardiographic findings of severe pulmonary regurgitation and right ventricular enlargement in *an adult patient* aged 50 years who underwent a surgical correction of TOF *when he was 10 years old*. The chronic severe pulmonary regurgitation made its impact with severe enlargement of right ventricle with associated systolic dysfunction.

The Electrocardiography (EKG) shows a right bundle branch block with a very wide QRS duration of 198 ms underscoring the right ventricular cardiomyopathy.

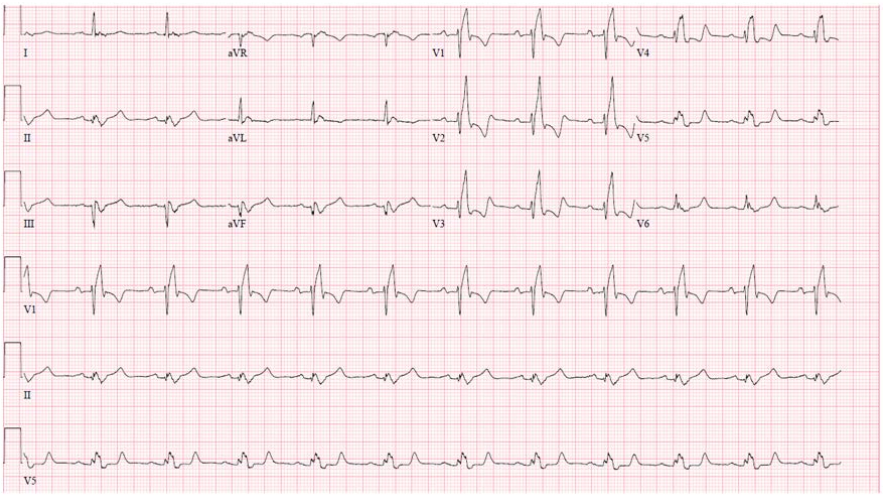

Image 1A, Video 1: Severe enlargement of right ventricular outflow tract (measuring 6.2 cm) is noted.

Image 1B, Video 2: is remarkable for massive enlargement and hypokinesis of right ventricle with septal flattening secondary to volume overload due to severe pulmonary regurgitation. Also noted is severely enlarged Right Atrium (RA). The Interatrial septum (IAS) bows to left due to higher right atrial pressure.

Image 1C, Video 3: Shown is the color comparison view of Pulmonary Valve (PV) (image is in diastole). Torrential pulmonary regurgitation is noted.

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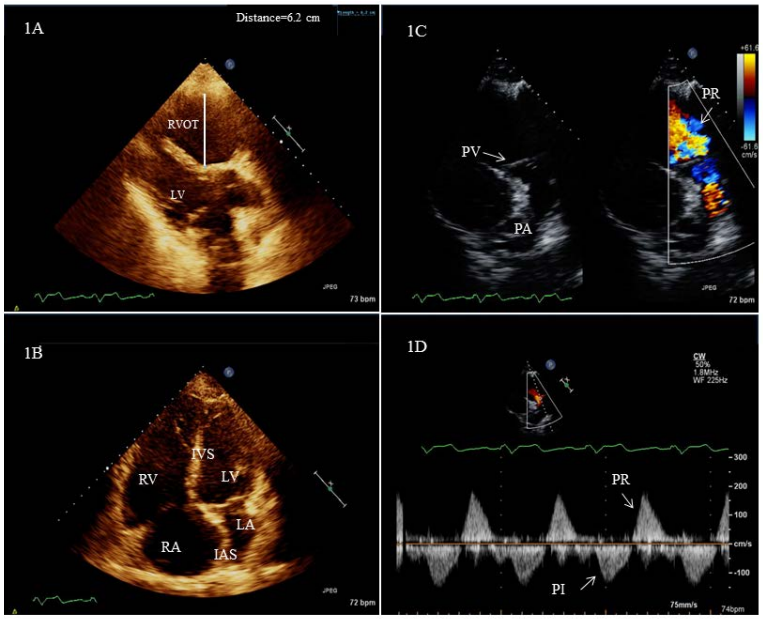
Image 1D: A continuous Doppler interrogation across the pulmonary valve shows the classic sine wave pattern of inflow and regurgitation across pulmonary valve with steep deceleration of pulmonary regurgitant waveform, characteristic of severe pulmonary regurgitation.



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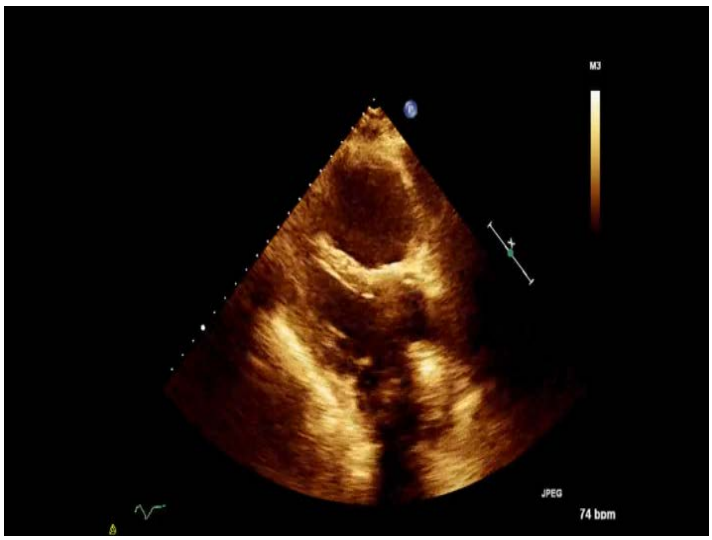

Video 1

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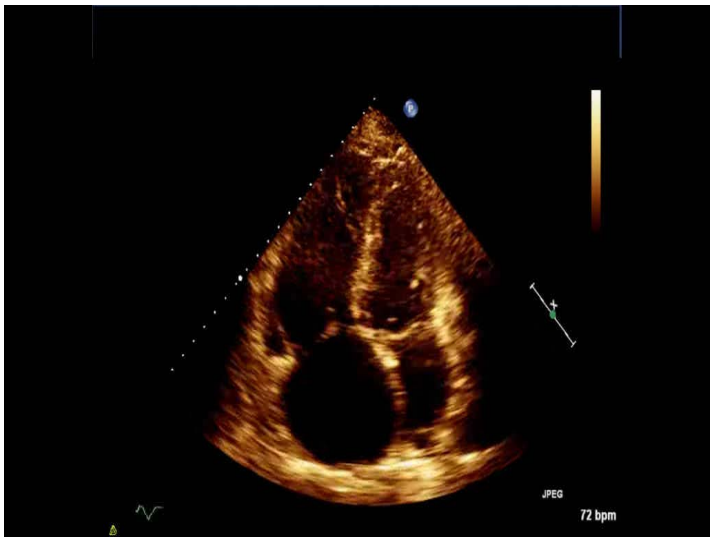
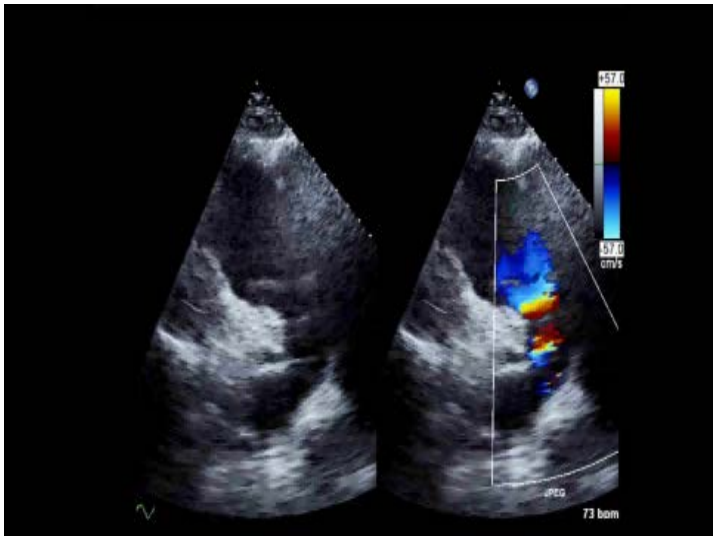


Video 2



Video 3

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

The patient has provided written permission for publication of the case detail.

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Research

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Biomarkers Score for Patients with Mitral Stenosis: A useful conjunction with Wilkins's Score for Early Intervention

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ABSTRACT

Objective: We proposed a novel new insight independent score of Mitral Stenosis (MS) based on elevated biomarkers.
Subjects and Methods: One hundred sixty-eight patients with MS candidate for Percutanous balloon valvuloplasty (PBMV) were included in the study. Brain Natriurectic Peptide (BNP), Tenascin-C (TN-C), copeptin and high-sensitive C-reactive protein (hs-CRP) were measured before PBMV. The cut-off value of each biomarker for prediction of systolic pulmonary artery pressure >50 mm Hg was calculated. Two points were given to a value ≥cut-off value and one point if less. Summation of points gave the biomarkers score.
Results: A biomarker score cut-off value ≥5.2 had a sensitivity of 83.6%, a specificity of 82.9% (AUC=0.85), in predicting cardiac events after successful PBMV. The Wilkins's score of ≥6.5 had a sensitivity of 73.5%, a specificity of 79.2% (AUC=0.80). The conjunction of Wilkins's score with biomarker score have higher predicting power (AUC=97%). The correlation co-efficient of biomarker score was (r=0.755), greater than that of the Wilkin's score (r=0.613). The combined biomarkers and Wilkins's score showed the strongest correlation with cardiac events (r=0.911). In multiple regression analysis, the regression co-efficient of biomarker score versus Wilkin's score was (0.595 *versus* 0.364), and the combined scores had the strongest powerful independent predictor of cardiac events (r=0.825).
Conclusions: In patients with MS especially asymptomatic patients, biomarker risk score that included BNP, tenacin-c, copeptin and hs-CRP and, had a good correlation with clinical outcomes after successful PBMV, and the conjunction of the biomarkers score and Wilkin's score provided higher prognostic value.

KEYWORDS: Wilkins's score; Biomarkers score; Mitral stenosis; Valvuloplasty.

ABBREVIATIONS: MS: Mitral Stenosis; PBMV: Percutanous balloon valvuloplasty; BNP: B-type natriuretic peptide; BMV: Balloon Mitral Valvuloplasty; MV: Mitral Valve; TN-C: Tenascin C; hs-CRP: High sensitive C-reactive protein; LA: Left Atrial; SPAP: Systolic Pulmonary Artery Pressure; PMV: Percutaneous mitral balloon valvuloplasty; EDTA: Ethylenediaminetetraacetic acid; ROC: Receivers Operating Characteristic.

INTRODUCTION

Rheumatic valvular heart diseases continue to be a major health problem in developing countries. Mitral stenosis is one of the most frequently encountered rheumatic valvular heart disease affections.[1,2] Mitral stenosis is a progressive disease, characterized by hemodynamic abnormalities as well as a rheumatic process,[3,4] causing progressive obstruction of left ventricular inflow. When the valve area decreases to <2 cm^2, subjects usually develop dyspnea with exertion as an initial symptom. Once this area falls to below 1.5 cm^2, intervention is of-

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ten necessary because of the intolerable symptoms, arrhythmia or pulmonary hypertension, especially in patients with a valve morphology suitable for PMBV.

Regular follow up for patients with significant mitral stenosis is crucial to take the proper decision of intervention in the proper time (either surgical replacement or alternatively balloon valvuloplasty if the valve morphology is suitable). It is frequently encountered that rheumatic MS patients describe equivocal symptoms. Due to the long latent period between onset of the initial rheumatic valvular affection and development of significant mitral stenosis, it is difficult for the treating physician to truly identify patients with symptoms that could be attributed to either hemodynamically significant stenosis or non cardiac dyspnea. Some patients who are considered asymptomatic adapt their level of exertion and thereby do not get symptoms. Symptomatic status is mainly subjective, and hence a better risk stratification objective tool is required to be implemented in regular follow up of rheumatic MS patients.[5]

The safety and success of Balloon Mitral Valvuloplasty (BMV) techniques is mostly dependent on the selection of patients. There are multiple predictors of the outcome, including age, functional class, previous commissurotomy, pre-procedure Mitral Valve (MV) area, valve anatomy, and balloon size used.[6] Brain natriuretic peptide (BNP) a useful biomarker would reflect disease severity, increase with progression of disease, reflect subclinical myocardial dysfunction, discriminate between patients in whom symptoms do and do not develop in the short to medium term, and be easily and reliably measured.[7]

Fibrotic changes in the heart and lung tissue are controlled by the activity of proteolytic enzymes, such as extracellular matrix-degrading metalloproteinases.[8] Matrix metalloproteinases can stimulate the secretion of TN-C, which acts as a strong mitogenic cofactor, leading to smooth muscle cell proliferation.[9] High sensitive C-reactive protein (hs-CRP) predicts morbidity and mortality in various clinical conditions. The effect of hs-CRP on progression of chronic rheumatic mitral stenosis may have a role, especially in developing atrial fibrillation and left atrial thrombi.

We hypothesize that biomarkers may be responsible for the progression of pulmonary hypertension and may be the cause beyond recurrence of symptoms or restenosis after successful PBMV. So we aimed to introduce a new insight of scoring regarding selection of patients with mitral stenosis for PBMV early, even in asymptomatic patients named (Biomarker score for PBMV).

PATIENTS AND METHODS

One hundred and sixty-eight patients with moderate to severe rheumatic mitral stenosis (MS) [MVA≤1.5 cm^2], were included in this study. All patients had suitable mitral valve scores for percutaneous dilation (mitral valve scores of ≤8).[10] Exclusion criteria were poor echocardiography window, significant renal impairment, presence of ischemic heart disease by history or resting wall motion abnormality on echo-Doppler study, previous cardiac surgery or valve intervention, coexistent heart muscle disease or other valvular lesion (if graded more than mild) or more, presence of Left Atrial (LA) thrombi. The study was approved by the local ethics committee, and written informed consent was obtained from all patients enrolled in the study.

ECHOCARDIOGRAPHIC EVALUATION

Comprehensive two-dimensional and color Doppler transthoracic echocardiogram was performed before PMV, using Vivid 7 instruments (GE Medical Systems, Milwaukee, Wisc., USA). The morphologic features of the mitral valve were categorized using the Wilkins echo score and the total echocardiographic score was obtained by adding the scores for leaflet mobility, thickness, calcification, and subvalvular lesions. Mitral Valve Area (MVA) was measured by direct planimetry in parasternal short-axis view, and continuous wave Doppler was used to calculate peak pressure gradient of tricuspid regurgitation. Mitral and tricuspid regurgitation were graded from 0 to 4+, depending on the spatial extent of the color flow jet area expressed as a percentage of the left or right atrial area. Systolic Pulmonary Artery Pressure (SPAP) was derived from the tricuspid regurgitant jet velocity (v) with the modified Bernoulli equation (4v2) and assuming a right atrial pressure of 10 mm Hg.[11] Patients were screened for left atrial thrombus with a two-dimensional transesophageal echocardiogram in the 24 h preceding the procedure. If thrombus was detected, the patient was not a candidate for PBMV. Transthoracic echocardiographic measurement of MVA and quantification of MR were repeated one day after Percutaneous mitral balloon valvuloplasty (PMV).

BIOCHEMICAL ANALYSIS

Brain Natriuretic Peptide Measurement

All samples were collected by veni-puncture into Ethylenediaminetetraacetic acid (EDTA) tubes within 2 hours of obtaining the baseline echocardiogram and one week after PMC (for group I). The blood samples were kept at room temperature and analyzed within 4 hours of sampling using the Triage BNP assay (Biosite diagnostics). Before analysis, each tube was inverted several times to ensure homogeneity. The BNP assay was a sandwich immuno-assay that consisted of a disposable device to which EDTA anticoagulated whole blood or plasma was added.

Serum Tenascin-C Measurement

Blood samples for TN-C were obtained before and 1 month after PMBV in the mitral stenosis group and obtained once in the control group. The blood samples for TN-C (ELISA kit for Human Tenascin, Uscn Life Science Inc., Wuhan, China) were obtained and centrifuged, then stored at -70 ºC until analy-

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sis in all study subjects. Serum TN-C levels were measured with the large subunit containing the C dominant of FN III repeats level using one-step sandwich enzyme immunoassay kits.

Serum copeptin Measurement

Blood samples for copeptin (ELISA kit for Human Copeptin, Uscn Life Science Inc., Wuhan, China) were obtained immediately before and 24 h after PBMV, centrifuged, then stored at -70 ºC until assayed. The detection limit of the assay was 7.4 pg/ml.

High Sensitive C-reactive Protein Analysis

Blood samples were centrifuged and the serum was stored at -70 ºC until analysis. High sensitivity C-reactive protein (hs-CRP) levels were measured using high sensitivity assay (N Latex CRP Mono; Dade Behring, Marburg, Germany) by means of particle-enhanced immunonephelometry using the Behring Nephlometer System that allows detection of levels as low as 0.175 mg/L.

Percutaneous mitral balloon valvuloplasty: All patients underwent complete diagnostic right and left heart catheterization before MBV. All patients were given intravenous heparin (100 U/kg) immediately after we achieved LA access by means of transseptal left heart catheterization. Mitral balloon valvuloplasty was performed via a transatrial approach using multitrack double balloon technique. Procedural success was defined as MVA≥1.5 cm^2 and MR≤2/4, as used by Song, et al.[12]

Clinical and Echocardiographic Follow-up

A detailed clinical and echocardiographic (2D, continuous-wave Doppler and color-flow imaging) assessment were conducted at every 3 months for the first year and at 6-month intervals thereafter, with a median duration of 31 (range 19-54) months. The predefined study endpoints were assessed: a composite clinical events endpoint including cardiovascular death, mitral valve re-intervention, newly developed atrial fibrillation (AF), progressive re-elevation of pulmonary artery pressure, and hospital readmission due to decompensated heart failure. The patients were divided into two groups (favorable and unfavorable) according to clinical events and the need for post-PBMV mitral re-intervention or surgery.

Statistical Analysis

All continuous variables are reported as mean±SD or as percentages. Analysis was done with SPSS 16.0 (SPSS, an IBM company; Chicago, Ill, USA). Receivers Operating Characteristic (ROC) curves were calculated to determine the best cut-off values of studied biomarkers for predicting sPAP ≥50 mm Hg. Receivers operating characteristic (ROC) curves were calculated to determine the best cut-off values of biomarker score and Wilkins's score in predicting cardiac events after PBMV. Associations of biomarker score and echocardiographic parameters with outcomes were evaluated by use of the Spearman correlation coefficient. Independent predictors of biomarker score were determined by means of multiple regression analysis. Standardized *B* regression coefficients and their significance as determined by multilinear regression analysis were reported.

RESULTS

The demographic, echocardiographic and biochemical variables are presented in Table 1.

Variable	
Age (years)	39.6±1.5
Male/Females	75/93
BSA (m^2)	1.67±0.85
Atrial fibrillation rhythm	25/168
NYHA Class	2.1±0.7
Systolic blood pressure (mmHg)	117±10
Diastolic blood pressure (mmHg)	70±5
Echo-score	5.6±1.9
MVA–2D planimetry (cm^2)	0.97±0.2
Mean transmitral gradient (mmHg)	15.9±5.6
LA antero-posterior diameter (mm)	50.1±0.55
LVEDD (mm)	43.2±0.5
LVESD (mm)	26.5±0.3
LVEF (%)	69.9±11.8
RV diastolic diameter (mm)	32.5±1.1
PAPs (mmHg)	67.5±24.2
Mitral regurgitation grade	0.81±0.63
Brain natriuretic peptide (pg/ml)	112.5±41.3
Tenascin-C (ng/ml)	18.0±4.1
Copetin (pg/ml)	69.5±31.8
hs-CRP (mg/l)	4.9±2.7

BSA: Body Surface Area; MVA: Mitral Valve Area; 2D: Two dimensional; LVEDD: Left Ventricular End Diastolic; LVESD: Left Ventricular End Systolic; PAPs: Pulmonary artery systolic pressure; hs-CRP: high sensitive C-reactive protein.

Table 1: Baseline demographic, echocardiograpic and biomarkers data of patients with mitral stenosis Included in the study.

Calculation of the Biomarker Score

ROC curve analysis demonstrates overall, the cut off value of BNP, tenacin-C, copeptin and hs-CRP were 75.0 pg/ml, 12.5 ng/ml, 70.0 ng/ml and 5.8 mg/l respectably showed the best sensitivity and specificity for predicting sPAP>50 mm Hg (Table 2). Then we gave two points for each marker for a value equal or more than the demonstrated cut-off value and one point for the value less than the cut-off value [the total score was 4-8 point], (Table 3). The echocardiographic variables in patients with MS were significantly improved after PBMV (Table 4). All patients had an echo score under 8, reflecting the selected nature of this population. Procedural success was achieved in 161of 168(96%)

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Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95% CI	P value
BNP (pg/ml)	≥75.0	80	73	0.72	0.63-0.82	<0.002
Tenacin-c (ng/ml)	≥12.5	82	50	0.73	0.64-0.82	<0.002
Copeptin (pg/ml)	≥70.0	76	64	0.69	0.58-0.80	<0.003
Hs-CRP (mg/l)	≥5.8	73	82	0.71	0.58-0.83	<0.002

BNP: Brain Natriuretic Peptide; Hs-CRP: high sensitive C-reactive protein.

Table 2: Validity of biomarkers cut-off values in predicting systolic pulmonary artery pressure ≥50 mm Hg in patients with mitral stenosis.

Biomarker	Cut-off value	Points
BNP level (pg/ml)	<75.0	1
	≥75.0	2
Tenascin-C (ng/ml)	<12.5	1
	≥12.5	2
Copeptin (pg/ml)	<70.0	1
	≥70.0	2
Hs-C-reactive protein (mg/l)	<5.8	1
	≥5.8	2
Total score		4-8

Table 3: Biomarker score for PBMV in patients with mitral stenosis.

Variable	Before PBMV	After PBMV	P-value
MVA–2D planimetry (cm^2)	0.97±0.2	2.2±0. 3	<0.001
Mean transmitral gradient (mmHg)	15.9±5.6	3.5±3.1	<0.0001
LA antero-posterior diameter (mm)	50.1±0.55	43.3±0.22	<0.02
LVEDD (mm)	43.2±0.5	43.5±0.7	>0.05
LVESD (mm)	26.5±0.3	26.3±0.6	>0.05
LVEF (%)	69.9±11.8	68.2±10.1	>0.05
RV diastolic diameter (mm)	32.5±1.1	24.7±0.6	<0.02
PAPs (mmHg)	67.5±24.2	33.7±15.2	<0.001

MVA: Mitral valve area; 2D: Two dimensional; LVEDD: Left ventricular end diastolic; LVESD: Left ventricular end systolic; PAPs: Pulmonary artery systolic pressure.

Table 4: Echocardiographic variables before and one day after percutaneous mitral valvuloplasty (PBMV).

patients, using the above-mentioned definition. The 7 inadequate immediate results were related to suboptimal valve opening (valve area <1.5 cm^2) in 6 cases and severe MR (grade≥3) in one cases.

During follow-up 67 patients developed unfavorable outcomes, (4 patients showed worsening of MR, 23 patients showed newly developed AF, 29 patients showed progressive re-elevation of pulmonary artery pressure and, 5 underwent repeat PBMV, and 6 hospital admissions due to decompensated heart failure). No valve replacement or death was recorded. Table 5 shows a comparison between patients with favorable *vs.* those with unfavorable outcomes after PBMV. The mean Wilkin's score was comparable between both groups (P>0.05), while the biomarker score was significantly elevated in those with unfavorable outcome (P<0.001).

The ability of biomarker score to predict patients with cardiac events was evaluated by means of ROC analysis (Figure 1). A biomarker score cut-off value ≥5.2 had a sensitivity of 83.6%, a specificity of 82.9% (AUC=0.85), in predicting cardiac events after successful PBMV. On the other hand the Wilkins's score of ≥6.5 had a sensitivity of 73.5%, a specificity of 79.2% (AUC=0.80), in predicting cardiac events. The conjunction of Wilkins's score with biomarker score have higher predicting power (AUC=97%) with a sensitivity of 92.4% and a specificity of 92.7%), (Table 6 and Figure 2) Table (7) shows the univariate and multivariate relationships of biomarker score and echocardiographic parameters to cardiac events during follow-up. In Spearman analysis, statistically significant correlations were found between biomarker score and other echocardiographic parameters. The correlation co-efficient of biomarker score was 0.755 (p<0.0001), greater than that of the Wilkins score (r=0.613,

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Variable	Favorable outcome group (N=94)	Unfavorable outcome group (N=67)	*P* value
Age	39.2±11	39.5±10	>0.05
LAD	49.8±1.2	5.2±1.2	<0.05
MVA	0.99±0.05	0.98±0.07	>0.05
Transmitral Mean PG	17.5±2.1	18.9±2.2	>0.05
RVD	3.1±0.4	3.2±0.2	>0.05
Pre- procedure MR	0.8±0.6	0.9±0.3	>0.05
PAPs (mmHg)	46.6±19.2	78.5+21.9	<0.01
Wilkin's score	5.4.2±1.2	5.8±1.1	>0.05
Biomarkers score	5.0±0.9	8.9±1.3	<0.001

MVA: Mitral Valve Area; RVD: Right Ventricular Diameter; MR: Mitral Regurgitation; PAPs: Systolic pulmonary artery pressure.

Table 5: Comparison between patients with favorable versus those with unfavorable outcomes after percutanous balloon mitral valvuloplasty.

Score	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95% CI	*P* value
Wilkin's score	≥6.5	73.5	79.2	0.80	0.69-0.92	<0.002
Biomarkers score	≥5.2	83.6	82.9	0.85	0.74-0.96	<0.001
(Wilkin's +biomarker) scores		92.4	92.7	0.97	0.96-1.00	<0.000

PBMV: Percutaneous balloon mitral valvuloplasty.

Table 6: Validity of Wilkins score, biomarkers score cut-off values as well as the compunction of both scores in predicting outcomes after PBMV.

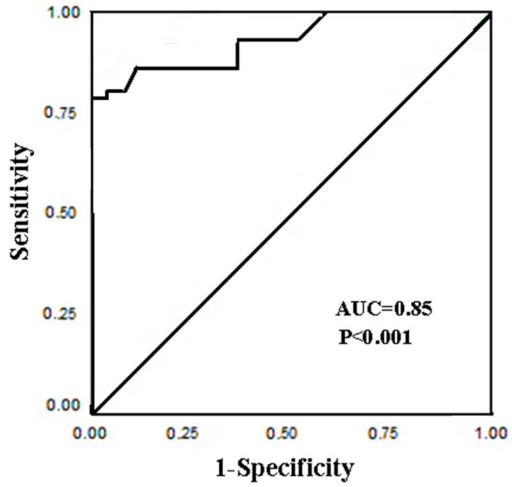

Figure 1: ROC curve for biomarker score showing sensitivity of 83.6% and specificity of 82.9% in predicting outcome after PBMV, at a cut off value of ≥5.2 mg/l (AUC at 95% CI=0.85(0.58-0.83).

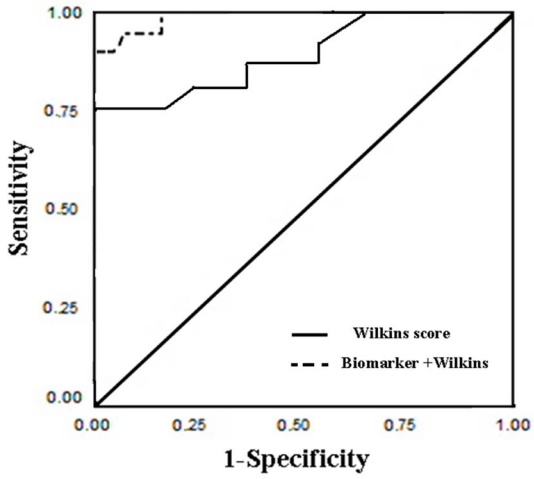

Figure 2: ROC curves for Wilkins score (AUC=0.80; 95% CI[0.74-0.96]) alone and the combined (Wilkins+biomarker scores) showing sensitivity of 92.4% and specificity of 92.7% for the combined scores in predicting outcome after PBMV (AUC at 95% CI=0.97(0.96-1.00).

Variable	Spearman coefficient	*P* value	standardized regression coefficient	*P* value
Wilkins score	0.613	<0.002	0.364	<0.01
Mitral valve area (cm²)	0.315	<0.004	--	
PAPs (mmHg)	0.460	<0.002	0.242	<0.04
Brain natriuretic peptide	0.495	<0.004	--	
Tenasin-c	0.583	<0.002	--	
Copeptin	0.492	<0.004	--	
High sensitive C-reactive protein	0.385	<0.003		
Biomarker score	0.755	<0.001	0.595	<0.001
Wilkins plus biomarker scores	0.911	<0.0001	0.825	<0.0001

Table 7: Univariate and Multivariate relationships of studied variables to cardiac events.

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p<0.002); MVA(r=0.312, p<0.02); sPAP(r=0.499, p<0.002). On the other hand the combined biomarkers and Wilkins's score showed the strongest correlation with cardiac events (r=0.911). In multiple linear regression analysis, the standardized regression coefficient (r=0.595) of biomarker score was much higher than those of Wilkin's score r=0.364), and the combined scores had the strongest powerful independent predictor of cardiac events after PBMV.

DISCUSSION

The present results showed that the efficacy of our biomarker risk score was superior to that of Wilkins score for prediction of cardiac events after successful PBMV for patients with moderate-severe MS. Moreover, a combination of both the risk scores provided higher prognostic value than the Wilkins score alone, for prediction of follow-up outcome after PBMV.

PBMV, is unique in that it provides dramatic hemodynamic and symptomatic relief as soon as it is carried out with success. Due to these sudden changes in hemodynamic and metabolic parameters in MS after PBMV, it has seemed to be highly attractive to investigate some characteristics of MS before and after the procedure.[13]

Compared to the Wilkins score, the biomarker score had several main advantages. (1) It provided complementary prognostic information to the Wilkins score for predicting follow-up outcome after PBMV, (2) The biomarker risk score could stratify risk among patients without symptoms and relatively low levels of Wilkins score. Precise prognostic information is important for tailoring treatment to individual patients and/or for facilitating the allocation of limited health care resources, (3) It could be argued that the biomarker risk score may be less influenced than Wilkins score by analytical and intra-individual variations, which might compromise the accuracy of prognostic assessments mild-moderate MS especially asymptomatic patients. (4) The risk score takes into account Natriuretic peptides, tenasin-C, copeptin and hs-CRP.

BNP seem to be very promising candidates, as there is great consistency on their ability to reflect the activity and progression, as well as to predict the prognosis.[14] Increased levels of TN-C have been found in rheumatic aortic valves and has a significant role in progression and severity of pulmonary hypertension.[15] The C-terminal part of the vasopressin prohormone (Copeptin) is measured easily and reliably.[16] As in chronic obstructive pulmonary disease, pulmonary hypertension is usually present in MS because of the increased left atrial pressure, pulmonary arteriolar constriction and obliterative changes in the pulmonary vascular bed.[13] hs-CRP is an important marker of chronic inflammatory process.

On the other hand, it was previously reported that TN-C had an increase in pulmonary hypertension.[17,18] Smooth muscle cell proliferation is one of the pathophysiologic roles of TN-C in pulmonary hypertension.[19,20] Higher TN-C levels were seen in patients with severe rheumatic mitral stenosis than in healthy subjects and TN-C was an independent predictor for mitral stenosis. After successful PBMV, there was a dramatic decrease not only in sPAP levels but also in TN-C levels.[21]

The present study found that the biomarker score was the strongest independent predictor of post PBMV outcome, with a best cut-off value being ≥5.2 mm Hg. The most commonly reported independent predictors of post-PMV clinical events (cardiovascular death, mitral valve surgery and repeat PMV) and restenosis are echo score and post-PBMV mitral valve area, both related to mitral valve anatomy.[22-25]

In mitral stenosis, pulmonary hypertension is due to three components: (1) passive, due to left atrial hypertension; (2) vasoreactive, due to pulmonary arteriolar constriction; and (3) due to structural changes in pulmonary vascular disease.[26,27] The first two are reversible, the first immediately after PMV and the second later, within a few months of intervention, while the third factor is permanent and does not usually regress.[28] Higher levels of CRP and others biomarkers may be responsible for atrial fibrosis. Such atrial fibrosis is supposed to be responsible for atrial fibrillation found in rheumatic mitral stenosis [29]

BNP and hs-CRP are important and may be sufficient, in assessment of activity and functional status. On the other hand TN-C and copeptin are largely associated with the progress of f pathologic changes and may give an idea about the early fibrotic changes in the pulmonary vasculature that may progress to irreversible pattern of pulmonary hypertension. Neuhold, et al.[30] reported that copeptin in chronic heart failure patients was superior to BNP and NT-proBNP for the prediction of all-cause mortality

For a proper selection of therapeutic strategy in patients with MS, clinical evaluation and assessment of MV anatomy are essential.[31-33] Transthoracic 2D echocardiography allows classification of patients into anatomic groups to predict immediate and long-term outcome.[34,35] Although most cardiologists use the Wilkin's score, several echocardiographic scoring systems have been suggested for evaluation of MV anatomy.[36-39] None of the available scores has been shown to be superior to any of the others.[40]

CLINICAL IMPLICATION

Our ability of doing biomarkers score will enhance the current evaluation of patients with MS and could be used in conjunction with Wilkins's score for proper selection and early intervention especially for asymptomatic moderate mitral stenosis Our proposed risk score is simpler to apply in asymptomatic patients with moderate MS. This facility might encourage broader implementation, because busy clinicians must typically priori-

tize multiple tasks. Therefore, we anticipate that our suggested risk score may be a valuable tool in clinical practice in the future.

CONCLUSION

In patients with mild-moderate mitral stenosis especially asymptomatic patients, biomarker risk score that included BNP, tenacin-c, copeptin and hs-CRP and, had a higher accuracy to that of Wilkins's score for predicting clinical outcomes after successful PBMV. A combination of the biomarkers score and Wilkins's score provided higher prognostic value for predicting clinical outcomes after successful PBMV.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Mini Review

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Pharmacological Agents in the Clinic: Trial and Error

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ABSTRACT

Following an explosion of molecular and cellular research in the last 50 years, the study of specific molecular targets in the context of heart failure has generated much excitement. With the incidence of heart failure rising worldwide, new pharmacological agents are eagerly anticipated as a key tool with the potential for significant impact. In this regard, the results of the keenly awaited Does Cyclosporine Improve Clinical Outcome in ST Elevation Myocardial Infarction Patients (CIRCUS) trial have just been made available. Despite a substantial programme of supporting experimental and preclinical evidence however, the results have proved negative. This is of great disappointment to the clinical and scientific community. Here, this is discussed in the context of previous studies and future directions explored.

TARGETING MYOCARDIAL REPERFUSION INJURY TO MITIGATE HEART FAILURE

Molecular treatment regimens were first introduced into standard clinical practice in the 1980's but have not changed substantially since.[1] Myocardial infarction is one of the most widespread causes of secondary events, heart failure and death[2,3] and patients with ST-segment Elevation Myocardial Infarction (STEMI) are a particularly high risk group. The extent of cell death in infarction i.e. infarct size, is suggested to be a major determinant in the likelihood of survival.[4-6] Since myocardial reperfusion injury contributes greatly to the final infarct size, treatments that mitigate this have garnered significant interest.

The trial discussed herein focuses on the use of cyclosporine, a pharmacologic inhibitor of cyclophilin D that is a major component of the mitochondrial Permeability Transition Pore (mPTP). In ischemic tissue, Adenosine triphosphate (ATP) is depleted and cell death ensues. Upon reperfusion, further injury occurs due to generation of reactive oxygen species and calcium cation overload in mitochondria. This results in opening of the mPTP and mitochondria dependent cell death.[7] Inhibition of cyclophilin D by cyclosporine and subsequently mPTP opening reduces the severity of myocardial reperfusion injury in animal models.[8-11] Cyclosporine is in fact already in use as an immunosuppressant in organ transplantation and autoimmune disorders, though associated with toxicity in chronic administration. Of further concern, it has also been shown to impede the compensatory hypertrophy of the remote noninfarcted myocardium by additionally inhibiting cyclophilin A and calcineurin.[12,13] However, these studies were conducted with multiple doses of cyclosporine; a single, lower dose of cyclosporine is sufficient to reduce infarct size without adverse consequences on compensatory remodelling.[14] Thus cardiac studies have used single, acute doses to minimise off-target effects while attempting to retain benefits.

CYCLOSPORINE PHASE II TRIALS

Initial results in a small phase II trial indicated a reduction in infarct size in STEMI patients when cyclosporine was administered immediately before reperfusion (primary Percutaneous Coronary Intervention; PCI), n=30 treated with cyclosporine, n=28 controls. The primary endpoint, infarct size, was assessed by measuring the cardiac injury biomarkers creatine

kinase (CK) and troponin I and by Magnetic Resonance Imaging (MRI) in 11 control and 16 cyclosporine treated patients. While creatine kinase levels were significantly reduced by cyclosporine treatment, troponin I was not. MRI showed a significant reduction in infarct size, but this did not translate into any improvement in left ventricular ejection fraction three months later.[15] A follow-up report on the same patient cohort at 6 months, showed a persistent reduction in infarct size in the cyclosporine treated group, with a minor reduction in diastolic Left Ventricular (LV) volume and a slight, though non-significant trend for reduced wall thickness. Similar to 3 months, cardiac function (ejection fraction) was not improved.[14] However in another trial, in conjunction with thrombolytic therapy in STEMI patients cyclosporine addition did not improve any outcomes tested up to 6 months (n=50, n=51 controls), nor was infarct size affected though this was measured only by creatine kinase release.[16]

CYCLOSPORINE PHASE III TRIAL: CIRCUS

A phase III trial was commenced with larger numbers; 395 patients in the cyclosporine group and 396 controls, to assess whether clinical outcomes were improved at 1 year.[17,18] The primary outcome was a combination of death, worsening of heart failure during the first admittance, rehospitalization and an increase of 15% or more in LV end diastolic volume. However, cyclosporine showed no benefit on these outcomes and cardiac function and remodelling (left ventricular ejection fraction and end-diastolic or systolic volumes) did not differ between treated and control groups.[17] Unfortunately infarct size was not reported in this study, although area at risk was estimated using angiography and was not changed.[17] Notably, in contrast to the phase II trial,[15] creatine kinase levels (a measure of cardiac damage and indirectly, infarct size) were not improved by cyclosporine treatment.[17]

Why the failure from phase II to III?

Discrepancies in the outcomes from phase II and III might be explained by a number of factors. First, the former was rather preliminary and carried out with very small numbers which limits statistical power and reproducibility. Secondly, key parameters such as infarct size and LV wall thickness that were measured in phase II are not yet reported or available for phase III, thus similar endpoints are not being compared. Given the potential deleterious effects of cyclosporine on compensatory hypertrophy in the remote myocardium, rigorous assessment of remote wall thickness and LV remodelling is particularly essential. In the 6 month follow-up from phase II, a small though non-significant decrease in wall thickness in remote myocardium was seen,[14] but was not reported at phase III with larger patient numbers.[17] This must be addressed to confirm that a single dose of cyclosporine does not impair reparative remodelling. In addition, values for LV mass are not available for either study, and this is an important parameter in assessing remodelling rather than relying solely on end-diastolic volumes. However, the authors state that a sub-population of phase III patients were selected to evaluate infarct size and LV remodelling in a more stringent manner[18] and publication of the results of these will permit more direct comparison and dissection of the reasons for failure in moving to phase III.

The formulation of cyclosporine used is also given weight as a confounding factor; previously being Sandimmune (Novartis, which uses Cremophor EL, a polyoxyethylated castor oil as a vehicle) and currently, CicloMulsion (NeuroVive Pharmaceutical, where the vehicle is a lipid emulsion). However, in contrast to the preliminary positive study[15] Sandimmune was shown to decrease maximal respiration in muscle, though was an effect of the vehicle control itself rather than cyclosporine.[19] In addition, it was not found to be cardioprotective or to reduce infarct size in humans[16] or pigs,[20] although it did reduce infarct size in rabbits.[21] With regards to CicolMulsion used in the recently reported negative study, lipid emulsion itself reduces infarct size and improves functional recovery to a greater extent than cyclosporine through inhibition of cyclophilin D, although downstream signalling events indicate divergent mechanisms in cardioprotection.[22] This would rather indicate that an improvement might be expected whether from cyclosporine, the vehicle itself or both, but this simply did not translate into the clinic. In addition, further confounding factors might also exist, for example, the effects of cyclosporine, cardioprotective or otherwise appear to be influenced by anaesthesia protocols.[20,21,23]

CLINICAL TRIALS: LOST IN TRANSLATION

The disappointing results of this trial also call into question the translational abilities of current pre-clinical protocols. Such testing rarely includes prevalent comorbidities and risk factors or existing clinical treatments; without this, the interactions and outcomes in humans cannot be predicted. Consideration of these interacting factors could in fact reveal a sub-population of patients that might benefit greatly from this treatment. In addition, drug delivery methods and formulations that are clinically the most practical and likely to be used should be closely recapitulated in animal models. Further, many of the primary and secondary outcomes measured in trials do not form part of pre-clinical studies. For reasons of cost, survival up to one year for example might not be preferred but how can mouse to man possibly translate when different end-points are measured?

Clinical trial design itself is a crucial factor and must be reflected in preclinical animal models. Selection of inclusion and exclusion criteria, along with primary and secondary outcome measurements can significantly alter trial results and outcomes must be used that are sufficiently powered by the sample size. In addition, transparent and full reporting of results from animal studies are key to improving translation. The recently published Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines for improving study design and reporting of animal studies are intended to do just this.[24]

More substantial target validation and mechanistic information across multiple model systems more relevant to the human heart failure and clinical environment is also required. A carefully selected panel of heart failure mouse models that incorporate common co-morbidities along with commonly used clinical measurements and outcomes must be used to provide a more reliable basis for further drug development. In parallel, use of human stem cell-derived cardiomyocytes can address the concern of translatability from mouse to man. Although a drawback of this is cellular immaturity, efforts are underway to better recapitulate more mature human myocardium and a number of usable models now exist such as Engineered Heart Tissue (EHTs) that better model many of the key characteristics of the intact human heart.[25,26]

A unified workflow prior to clinical trials with worldwide input and adherence would also provide a much improved and clear pathway from target identification to the patient. Indeed, such approaches now exist in the US and recommendations for generating similar in Europe have been recently proposed.[27,28] Computational tools also provide an unprecedented resource that should be fully utilised.[1]

Finally, an important point to consider is simply that targeting opening of the mPTP alone is not sufficient to prevent progression to heart failure in some settings, discussed below.

TARGETING CELL DEATH TO MITIGATE HEART FAILURE

It has been noted that the results of the recently completed Cyclosporine A in Reperfused Acute Myocardial Infarction (CYCLE) study using Sandimmune are expected imminently although the primary end point is ST-segment resolution rather than clinical outcomes.[29] These authors also propose that discovery of more specific inhibitors of mPTP opening might yield more promising results.[29] Perhaps however, the opposite might be required. In considering cell death, cardiomyocyte loss is a defining feature not only of infarction (acute, high levels of cell death) but of heart failure in general (chronic, low levels of cell death).[30] 'Apoptotic' cell death, measured by Deoxyribonucleic acid (DNA) fragmentation and caspase activity is prevalent in the failing heart[31-33] in addition to 'necrotic' cell death, inferred on the basis of reparative fibrosis and a diffuse smearing pattern of DNA, suggesting the contributions of multiple mechanisms for cell death in end-stage heart failure.[32] Further, it has been suggested that chronic, low levels of cardiomyocyte death are equally, if not more so, deleterious to heart function than acute high levels of cell death associated with myocardial ischemia and reperfusion injury. Up to 50% of LV cardiomyocytes can be lost in ischemia before heart failure occurs, while only up to 20% of sporadic myocyte loss/dropout is required in the setting of pressure overload.[34] In addition, chronic low levels of sporadic cardiac muscle cell death are sufficient to cause heart failure in mice, and inhibition of caspase-dependent cell death in this model was protective.[35] Diverse gain- or loss-of-function mutations and pharmacological interventions in murine models directly implicate cell-death signaling pathways as relevant therapeutic targets in reducing the inexorable progression to heart failure.[36]

In conclusion, in the setting of acute infarction, a pharmacological agent that inhibits cell death, salvages jeopardized myocardium and reduces infarct size would be expected to prove highly effective. However, the outcome of the recent cyclosporine trial would indicate otherwise.[17] It should be noted that cyclosporine only targets one aspect of cell death[37] and that heart failure incorporates multiple aspects.[36] A dual inhibitor or combined inhibitors targeting both mitochondria dependent and independent cell death might provide a more productive method than either alone to significantly impact on heart failure progression. Even if early, acute cell death is limited during reperfusion, subsequent chronic, low levels of cell death will still contribute significantly to ensuing heart failure and death. Inhibition of both acute and chronic, ongoing sporadic cell death should therefore be targeted.

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