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RODOLFO DE PAULA LUSTOSA

***GLOBAL WORK EFFICIENCY* E PROGNÓSTICO A LONGO PRAZO EM
PACIENTES COM INFARTO AGUDO DO MIOCÁRDIO COM SUPRADESNÍVEL
DO SEGMENTO ST**

RIO DE JANEIRO

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Dissertação de Mestrado apresentada
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requisito à obtenção do título de Mestre
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Orientadores:

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Prof. Dr. Jeroen J. Bax

Dra. Victoria Delgado

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Dra. Victoria Delgado

Aprovada em 17 de Março de 2021

Banca Examinadora:

Profº Dr. Daniel Arthur Barata Kasal
Membro interno
Instituto Nacional de Cardiologia (INC)

Profº Dra. Ana Paula Siciliano
Membro externo
Instituto Nacional de Cardiologia (INC)

Profº Dra. Helena Cramer Veiga Rey
Membro interno
Instituto Nacional de Cardiologia (INC)

Profº Dr. Angelo Salgado
Membro interno (Suplente)
Instituto Nacional de Cardiologia (INC)

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RESUMO

LUSTOSA, Rodolfo de Paula. *Global work efficiency* e prognóstico a longo prazo em pacientes com infarto agudo do miocárdio com supradesnível do segmento ST. Rio de Janeiro 2021.

INTRODUÇÃO: O *strain* global longitudinal (SGL) do ventrículo esquerdo (VE) tem demonstrado valor prognóstico adicional sobre a fração de ejeção (FE) do VE em pacientes com infarto agudo do miocárdio com supradesnível do segmento ST (IAMCSST). Entretanto, o SGL não leva em consideração o efeito da pós-carga. Novos índices da função cardíaca baseados no trabalho miocárdico integram as medidas da pressão arterial (pós-carga) com SGL.

OBJETIVO: Investigar o valor prognóstico do *global work efficiency* (GWE) (refletindo a performance do VE) em pacientes com IAMCSST, através da obtenção de curvas pressão-*strain* ao ecocardiograma.

MÉTODOS: Um total de 507 pacientes com IAMCSST (média de idade 61±11 anos, 76% sexo masculino), foram retrospectivamente analisados. FEVE e GWE foram medidos pelo ecocardiograma nas primeiras 48 horas de admissão. GWE foi definido como a razão entre o trabalho construtivo dividido pela soma do trabalho construtivo e do trabalho desperdiçado em todos os segmentos do VE, e expresso em percentagem. Uma análise pela curva *spline* foi utilizada para definir a associação entre GWE reduzido e mortalidade global.

RESULTADOS: Após uma mediana de seguimento de 80 meses (intervalo interquartil 67-97 meses), 40 (8%) pacientes morreram. Pacientes com GWE reduzido (<86%) mostraram risco elevado para mortalidade global (17.5% vs. 4.7%; log-rank $p < 0.001$) em comparação com pacientes com GWE preservado ($\geq 86\%$). GWE reduzido (<86%) demonstrou uma associação independente com mortalidade global (HR 3.167; 95%IC 1.679-5.972; $p < 0.001$).

CONCLUSÃO: GWE reduzido (<86%) medido pela ecocardiografia transtorácica nas primeiras 48 horas de admissão em pacientes com IAMCSST foi associado com pior prognóstico a longo prazo.

Palavras-chave: Infarto agudo do miocárdio com supradesnível do segmento ST, eficiência global do trabalho miocárdico do ventrículo esquerdo, prognóstico.

ABSTRACT

LUSTOSA, Rodolfo de Paula. Global work efficiency and long-term prognosis in patients after ST-segment elevation myocardial infarction. Rio de Janeiro 2021.

INTRODUCTION: Left ventricular (LV) global longitudinal strain (GLS) has demonstrated incremental prognostic value over LV ejection fraction (EF) in patients with ST-segment elevation myocardial infarction (STEMI). However, LV GLS does not take into consideration the effect of afterload. Novel speckle tracking echocardiographic indices of myocardial work integrate blood pressure measurements (afterload) with LV GLS.

OBJECTIVE: The present study aimed to investigate the prognostic value of global work efficiency (GWE) (reflecting LV performance) obtained from pressure-strain loops with echocardiography in patients with STEMI.

METHODS: A total of 507 STEMI patients (mean age 61 ± 11 years; 76% male), were retrospectively analyzed. LVEF and GWE were measured by transthoracic echocardiography within 48 hours of admission. GWE was defined as the ratio of constructive work divided by the sum of constructive and wasted work in all LV segments, and expressed as a percentage. Spline curve analysis was used to define the association between reduced GWE and all-cause death.

RESULTS: After a median follow-up of 80 months (interquartile range 67-97 months), 40 (8%) patients died. Patients with reduced GWE (<86%) showed higher cumulative rates of all-cause mortality (17.5% vs. 4.7%; log-rank $p < 0.001$) in comparison with patients with preserved GWE ($\geq 86\%$). Reduced GWE (<86%) showed an independent association with all-cause mortality (HR 3.167; 95%CI 1.679-5.972; $p < 0.001$).

CONCLUSIONS: Reduced GWE (<86%) measured by transthoracic echocardiography within 48 hours of admission in STEMI patients is associated with worse long-term survival.

Key Words: ST-segment elevation myocardial infarction, global left ventricular myocardial work efficiency, prognosis.

LISTA DE FIGURAS

FIGURA 1: CÁLCULO DO <i>GLOBAL WORK EFFICIENCY</i> DO VENTRÍCULO ESQUERDO.....	18
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LISTA DE ABREVIATURAS E SIGLAS

ATP	Adenosina trifosfato
DAC	Doença arterial coronariana
DCV	Doença cardiovascular
FE	Fração de ejeção
FEVE	Fração de ejeção do ventrículo esquerdo
GCW	<i>Global constructive work</i>
GLS	<i>Global longitudinal strain</i>
GLVMWE	<i>Global left ventricular myocardial work efficiency</i>
GRACE	<i>Global Registry of Acute Coronary Events</i>
GWE	<i>Global work efficiency</i>
GWI	<i>Global work index</i>
GWW	<i>Global wasted work</i>
IAM	Infarto agudo do miocárdio
IAMCSST	Infarto agudo do miocárdio com supradesnível do segmento ST
LV	<i>Left ventricular</i>
LVEF	<i>Left ventricular ejection fraction</i>
LVEDV	<i>Left ventricular end-diastolic volume</i>
LVESV	<i>Left ventricular end-systolic volume</i>
LV GLS	<i>Left ventricular global longitudinal strain</i>
SGL	<i>Strain global longitudinal</i>
TIMI	<i>Thrombolysis in myocardial infarction</i>
VE	Ventrículo esquerdo

SUMÁRIO

INTRODUÇÃO.....	11
REFERENCIAL TEÓRICO.....	13
2.1 INFARTO AGUDO DO MIOCÁRDIO COM SUPRADESNÍVEL DO SEGMENTO ST (IAMCSST).....	13
2.2 VALOR PROGNÓSTICO DO ECOCARDIOGRAMA EM PACIENTES COM IAMCSST.....	14
2.3 TRABALHO MIOCÁRDICO.....	16
2.4 APLICAÇÕES CLÍNICAS DO TRABALHO MIOCÁRDICO MEDIDO PELA ECOCARDIOGRAFIA.....	18
JUSTIFICATIVA.....	21
REFERÊNCIAS BIBLIOGRÁFICAS.....	22
APÊNDICE.....	26.

INTRODUÇÃO

A doença isquêmica do coração permanece como uma importante causa de morte pelo mundo (1) e pacientes com infarto agudo do miocárdio apresentam um risco adicional de eventos cardiovasculares, incluindo insuficiência cardíaca (2). Tamanho do infarto, assim como dilatação e disfunção do ventrículo esquerdo aumentam o risco de insuficiência cardíaca e mortalidade cardiovascular (3). Na prática clínica, a avaliação da função sistólica do ventrículo esquerdo pela fração de ejeção (FE) do ventrículo esquerdo (VE) permanece amplamente reconhecida como um marcador prognóstico (4). Entretanto, suas limitações são bem conhecidas (como reprodutibilidade limitada, suposições geométricas) (5).

Recentemente, o *strain* global longitudinal (SGL), índice de função sistólica derivado da ecocardiografia bidimensional, demonstrou valor adicional sobre a FE para prever prognóstico após infarto agudo do miocárdio (IAM) com supradesnível do segmento ST (IAMCSST) (6, 7). Entretanto, ambos FEVE e SGL são parâmetros dependentes da pós-carga e sua avaliação pode ser influenciada pela frequência cardíaca e pressão arterial sistólica, que também são associadas a desfechos após IAMCSST (8-10).

A avaliação dos índices de trabalho miocárdico baseados na ecocardiografia bidimensional leva em consideração as condições de carga integrando a medida da pressão arterial com SGL para o cálculo da curva de pressão-*strain* (11). Especificamente, *global work efficiency* (GWE), combina as medidas de trabalho construtivo e trabalho desperdiçado e fornece informação sobre a performance global do ventrículo esquerdo. Entretanto, a associação desse novo parâmetro com desfechos após IAMCSST não foi estudado. O objetivo desse estudo foi investigar o

valor prognóstico do GWE, obtido pela curva pressão-*strain* com o ecocardiograma, em pacientes com IAMCSST.

REFERENCIAL TEÓRICO

2.1 Infarto agudo do miocárdio com supradesnível do segmento ST (IAMCSST)

As doenças cardiovasculares (DCVs) permanecem como a principal causa de morte no mundo (12). Em 2015, estima-se que 17.9 milhões de pessoas morreram decorrentes de DCVs (13). Sua relevância pode ser mensurada pelos impactos econômicos provocados pelo tratamento da doença. Na Europa, estima-se que as DCVs tem um custo de 169 milhões de euros anualmente sendo a doença arterial coronariana responsável por 27% desses custos (14).

No Brasil, as DCVs permanecem como um problema semelhante. Em 2011, 384.615 mortes foram atribuídas as DCVs, sendo a doença arterial coronariana (DAC) responsável por 31% dessas mortes (15) resultando em um déficit econômico da ordem de 4.18 bilhões de dólares na economia brasileira de 2006 até 2015 (16).

Devido ao avanço tecnológico no tratamento e acompanhamentos dos pacientes com IAM, há uma tendência de redução da mortalidade (17). O conhecimento da doença, dos fatores de risco e os avanços na multimodalidade de imagem cardiovascular possibilitaram a identificação de pacientes com alto risco para eventos (18).

Segundo a quarta definição universal de IAM, IAM tipo 1 (no qual se enquadra o IAMCSST), se define como aumento dos níveis de troponina acima do percentil 99 e acompanhado de pelo menos um dos seguintes critérios: sintomas de isquemia miocárdica aguda, alterações isquêmicas no eletrocardiograma, desenvolvimento de

onda Q patológica, imagem evidenciando perda de miocárdio viável ou nova alteração regional na mobilidade de parede consistente com etiologia isquêmica e identificação de trombo coronariano pela angiografia ou por autópsia (19). Pela diretriz da sociedade europeia de cardiologia (1), os métodos de imagem em pacientes com IAMCSST são indicados na apresentação, durante a hospitalização e antes da alta. No contexto pré-alta, o ecocardiograma estaria indicado em pacientes com FEVE \leq 40% e repetir 6 a 12 semanas após o infarto do miocárdio para avaliar a potencial necessidade de prevenção primária com cardiodesfibrilador implantável.

Dessa forma, considerando o problema de saúde representado pelo IAMCSST, torna-se fundamental o uso de novas ferramentas diagnósticas para a melhor compreensão da função ventricular e como novas tecnologias em imagem cardiovascular podem ajudar a identificar pacientes em risco. Nesse contexto, o ecocardiograma se torna uma ferramenta fundamental dentro dos métodos de imagem disponíveis por sua segurança, mínimo efeito de radiação e baixo custo em comparação com outros métodos disponíveis (20).

2.2 Valor prognóstico do ecocardiograma em pacientes com IAMCSST

O uso do ecocardiograma na prática clínica em pacientes com IAMCSST está relacionado a detecção de complicações relacionadas ao IAMCSST como disfunção mecânica (insuficiência cardíaca, aneurisma ou ruptura do miocárdio, disfunção do músculo papilar), complicações trombóticas (trombo mural) e complicações inflamatórias (pericardite) (21).

No ecocardiograma, após excluídas as complicações mecânicas relacionadas a doença, a medida da FEVE tem papel fundamental na avaliação dos pacientes com

IAMCSST. O método de escolha recomendado para a medida da FEVE é o método biplanar de Simpson (22). Sua importância prognóstica em pacientes com IAMCSST está reportada em estudos anteriores. Perelshtein Brezinov et al. (23) mostraram em uma coorte de 8983 pacientes admitidos com infarto agudo do miocárdio uma taxa de mortalidade de 36% em pacientes com FEVE < 30%. Bedetti et al (24) em uma coorte de 470 pacientes demonstraram que parâmetros ecocardiográficos como a FEVE adicionou valor prognóstico aos tradicionais métodos clínicos de estratificação como os escores TIMI (Thrombolysis In Myocardial Infarction) e o GRACE (Global Registry In Acute Coronary Events). Entretanto, a FEVE tem suas limitações pois nem sempre reflete um resumo apropriado do status da circulação. Os volumes medidos pelo método de Simpson e conseqüentemente a FEVE podem sofrer alterações de acordo com pré-carga, pós-carga e contratilidade (5).

Recentemente, novas tecnologias na ecocardiografia vem sendo empregadas para a avaliação da função ventricular e com impacto prognóstico no IAM entre elas o *strain*, *strain rate* e *speckle tracking*. *Strain* representa a deformação de um tecido quando a ele é aplicada determinada força, sendo medido em forma percentual. *Strain rate* é a medida da velocidade de deformação entre dois pontos (cm/s). O *speckle tracking* compara quadro-a-quadro a posição do ponto brilhante causado pela reflexão do ultrassom com o miocárdio, analisando a deformidade a partir do método bidimensional (25). O *strain* longitudinal está reduzido em pacientes com infarto, correlacionando-se com o tamanho do infarto e a FEVE (26). Seu uso na prática clínica também tem relação com prognóstico. Stanton et al (27) demonstraram em uma coorte de 546 indivíduos que foram submetidos ao ecocardiograma para avaliação da função ventricular que o *strain* foi superior a FEVE como preditor de eventos. Em outro estudo com 1.065 pacientes com insuficiência cardíaca com FEVE reduzida (28) o *strain* foi

um preditor independente de mortalidade. Entretanto, assim como ocorre com a FEVE, o *strain* também pode ser influenciado por alterações na pré e pós-carga (29) e estudos tem demonstrado valores de referência diferentes entre as diferentes fabricantes (30).

2.3 Trabalho miocárdico

O conceito das curvas de pressão-volume é amplamente usado na fisiologia cardiovascular e para avaliação da função cardíaca (31-33). Trabalhos experimentais já demonstraram ser possível avaliar a performance global dos ventrículos sem a influência das condições de pré e pós carga através de um índice de contratilidade que independe das condições de carga. Esse conceito não se tornou “padrão ouro” na prática clínica e na pesquisa devido ao fato de que técnicas invasivas são necessárias para determinação dessas curvas. Entretanto, a estimativa não invasiva dessas curvas já se mostrou como um forte preditor de eventos independente da FEVE como mostrado no estudo de Spevack et al (34).

De acordo com o mesmo princípio das curvas de pressão-volume, em 2012 foi publicado por Russell et al (11) o conceito da avaliação não invasiva do trabalho cardíaco. Segundos os autores, a determinação pelo ecocardiograma da área da curva pressão-*strain* refletiria o trabalho miocárdico e o consumo de oxigênio. Atualmente, o cálculo do trabalho cardíaco pelo ecocardiograma é realizado utilizando um software comercialmente disponível (EchoPac, GE sistemas médicos). Os índices de trabalho cardíaco são estimados através da combinação da estimativa não invasiva do pico da pressão do VE utilizando as medidas da pressão arterial com o esfigmomanômetro (no qual se assume que o pico sistólico da pressão do VE é igual

ao pico da pressão sistólica arterial) combinando com os dados ecocardiográficos de curvas do *strain*.

Após calcular o *strain* e introduzir os valores da pressão arterial obtidos pelo esfigmomanômetro, os tempos de abertura e fechamento das válvulas aórtica e mitral são identificados pelo ecocardiograma na janela apical 3 câmaras. Uma curva pressão-*strain* do VE é então construída com os dados do *strain* de todo o ciclo cardíaco, de acordo com o tempo de duração do relaxamento e contração isovolumétrica, das fases de ejeção e enchimento definidas pelos tempos de abertura e fechamento das válvulas aórtica e mitral e dos valores da pressão arterial (35).

O trabalho do ventrículo esquerdo é calculado como um produto entre a taxa de encurtamento segmentar e a pressão instantânea do VE. Os seguintes índices são derivados da medida do trabalho cardíaco pelo ecocardiograma (**Figura 1**):

- *Global work index* (GWI): trabalho total calculado do fechamento da válvula mitral até a abertura da válvula mitral representando a área da curva fornecida pelo software (valor em mmHg%);

- *Global constructive work* (GCW): trabalho realizado por um segmento durante o encurtamento na sístole e adicionando trabalho negativo durante o alongamento na diástole que representa o trabalho que contribui para a contratilidade miocárdica (valor em mmHg%);

- *Global wasted work* (GWW) : trabalho negativo realizado por um segmento durante seu alongamento na sístole e adicionando trabalho realizado durante o encurtamento na diástole que representa o trabalho que não contribui para a contratilidade miocárdica (valor em mmHg%);

- *Global work efficiency* (GWE): relação do GCW dividido pela soma de GCW e GWW e representa a medida de performance do VE (valor em %).

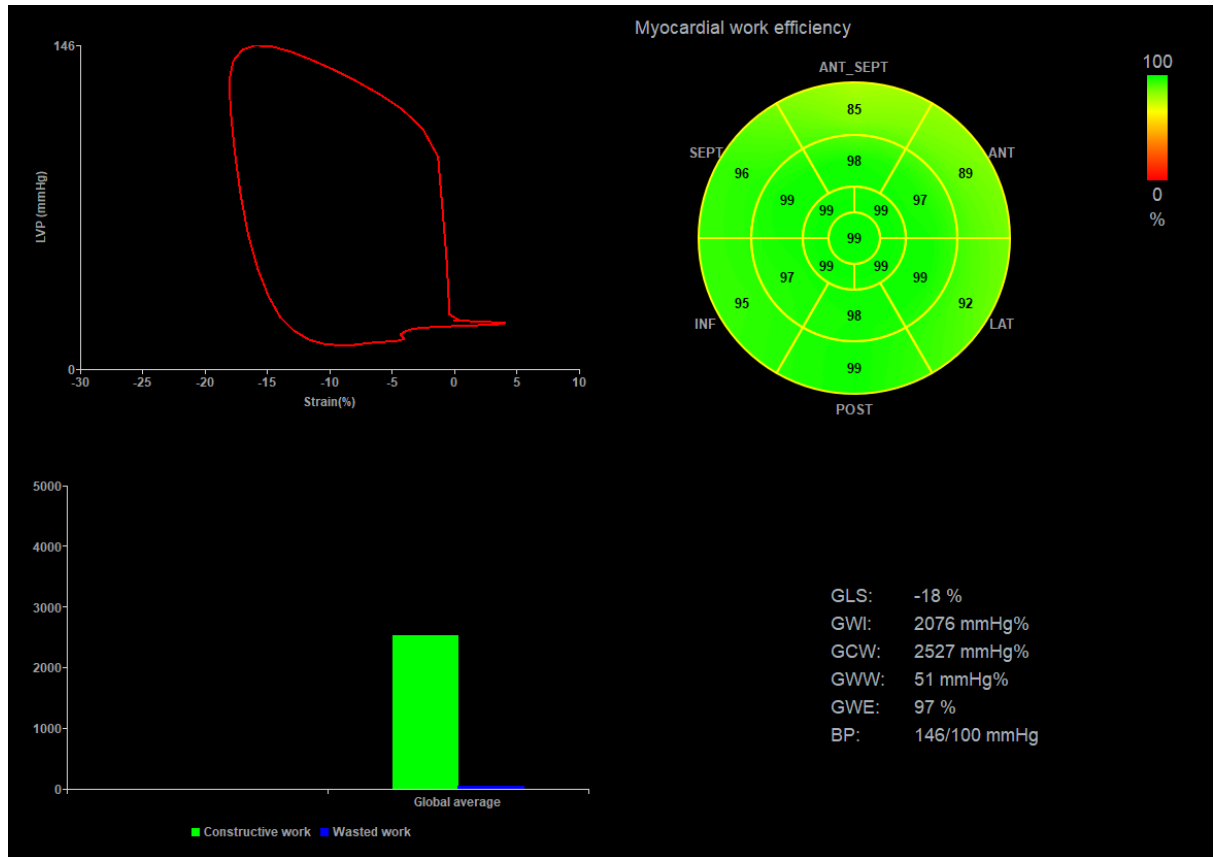


Figura 1: Cálculo do GWE do ventrículo esquerdo. Modelo de 17 segmentos mostrando os valores segmentares do GWE. Valores segmentares de GWE preservados são apresentados em verde e expressos em %. Os valores do índice de trabalho global, trabalho construtivo, trabalho desperdiçado, GWE e pressão arterial do paciente são mostrados em branco. GWE: *Global work efficiency*. (Fonte: o autor).

2.4 Aplicações clínicas do trabalho miocárdico medido pela ecocardiografia

Os primeiros trabalhos sobre a aplicação clínica da medida do trabalho cardíaco pelo ecocardiograma vieram em pacientes com insuficiência cardíaca (IC)

com indicação de terapia de ressincronização cardíaca (TRC). Galli et al (36) demonstraram em uma coorte de 97 pacientes com IC sintomática e indicação de TRC que pacientes com altos valores de GCW (trabalho construtivo) exibiam uma favorável resposta a TRC. Em outro estudo (37) os autores demonstraram que a medida do GCW e GWW (trabalho desperdiçado) poderiam fornecer uma melhor compreensão do mecanismo do dissincronismo ventricular e aumentar a identificação de pacientes que responderiam a TRC. Kostyukevich et al (38) demonstraram em uma coorte de 168 pacientes com IC e indicação de TRC que havia diferença significativa entre os valores regionais de GCW e GWW entre pacientes respondedores e não-respondedores a TRC. Van der Bijl et al (39) demonstraram que valores baixos de GWE medido antes da TRC foi independentemente associado com melhor prognóstico uma vez que a TRC poderia promover aumento da eficiência miocárdica.

No contexto das cardiopatias, Galli et al (40) evidenciaram que GCW era significativamente reduzido em pacientes com cardiopatia hipertrófica apesar da FEVE normal e era associado a fibrose visualizada na ressonância magnética cardíaca. Em outro estudo, Hiemstra et al (41) também demonstraram que os índices de trabalho cardíaco eram reduzidos na cardiopatia hipertrófica não obstrutiva e eram associados a desfechos. Clemmensen et al (42) demonstraram que pacientes com amiloidose apresentavam reduzidos valores de GWI (trabalho total) em comparação com indivíduos saudáveis e que no exercício essas diferenças eram mais pronunciadas.

Nas síndromes coronarianas agudas, Boe et al (43) demonstraram que a presença de valores regionais reduzidos de GWI poderiam identificar oclusão coronariana em pacientes com infarto agudo do miocárdio sem supradesnível do segmento ST. Em pacientes com IAMCSST, El Mahdiui et al (44) evidenciaram que

GWE era reduzido em pacientes com IC e FE reduzida pós IAMCSST em comparação com indivíduos saudáveis e indivíduos com fatores de risco para DCVs. Lustosa et al (45) demonstraram em uma coorte de 600 pacientes pós IAMCSST que os índices de trabalho cardíaco eram reduzidos 3 meses após o evento índice em pacientes que apresentaram remodelamento ventricular.

JUSTIFICATIVA

A relevância clínica do estudo se baseia no papel da estimativa não invasiva das curvas pressão-*strain* em pacientes com IAMCSST. Esta nova tecnologia foi validada há 8 anos e as evidências de sua aplicação na prática clínica vem crescendo na literatura. O presente estudo vem contribuir para estas evidências pela caracterização da função sistólica ventricular através do cálculo pela ecocardiografia transtorácica bidimensional da eficiência do trabalho global do VE (GWE) em pacientes com IAMCSST e sua relação com mortalidade.

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APÊNDICE 1: ARTIGO ORIGINAL

Global left ventricular myocardial work efficiency and long-term prognosis in patients after ST-segment elevation myocardial infarction

Running Title: *Lustosa et al; GLVMWE and prognosis in STEMI*

Authors: Rodolfo P. Lustosa, MD^{1,2}; Steele C. Butcher MD^{1,3}; Pieter van der Bijl, MD, PhD¹; Mohammed El Mahdiui, MD¹; Jose M. Montero-Cabezas, MD¹; Marina V. Kostyukevich, MD, PhD¹; Andrea Rocha De Lorenzo, MD, PhD²; Juhani Knuuti, MD, PhD⁴; Nina Ajmone Marsan, MD, PhD¹; Jeroen J Bax, MD, PhD¹; Victoria Delgado, MD, PhD¹.

From: ¹Department of Cardiology, Heart Lung Center, Leiden University Medical Center, Leiden, The Netherlands; ²National Institute of Cardiology (INC), Rio de Janeiro, RJ, Brazil; ³Department of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia; ⁴Department of Clinical Physiology, Nuclear Medicine and PET, Turku University Hospital and Turku PET Centre, University of Turku, Turku, Finland.

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Address for correspondence: Victoria Delgado, MD, PhD; Department of Cardiology, Heart Lung Center, Leiden University Medical Center; Albinusdreef 2 2300 RC, Leiden; The Netherlands; Phone: +31 71 526 20 20; FAX: +31 71 526 6809; E-mail: v.delgado@lumc.nl

Subject terms: Echocardiography, imaging, prognosis.

ABSTRACT

Background: Left ventricular (LV) global longitudinal strain (GLS) has demonstrated incremental prognostic value over LV ejection fraction (EF) in patients with ST-segment elevation myocardial infarction (STEMI). However, LV GLS does not take into consideration the effect of afterload. Novel speckle tracking echocardiographic indices of myocardial work integrate blood pressure measurements (afterload) with LV GLS. The present study aimed to investigate the prognostic value of global LV myocardial work efficiency (GLVMWE) (reflecting LV performance) obtained from pressure-strain loops with echocardiography in patients with STEMI.

Methods: A total of 507 STEMI patients (mean age 61 ± 11 years; 76% male), were retrospectively analyzed. LVEF and GLVMWE were measured by transthoracic echocardiography within 48 hours of admission. GLVMWE was defined as the ratio of constructive work divided by the sum of constructive and wasted work in all LV segments and expressed as a percentage. Spline curve analysis was used to define the association between reduced GLVMWE and all-cause death.

Results: After a median follow-up of 80 months (interquartile range 67-97 months), 40 (8%) patients died. Patients with reduced GLVMWE (<86%) showed higher cumulative rates of all-cause mortality (17.5% vs. 4.7%; log-rank $p < 0.001$) in comparison with patients with preserved GLVMWE ($\geq 86\%$). Reduced GLVMWE (<86%) showed an independent association with all-cause mortality (HR 3.167; 95% CI 1.679-5.972; $p < 0.001$).

Conclusions: Reduced GLVMWE (<86%) measured by transthoracic echocardiography within 48 hours of admission in STEMI patients is associated with worse long-term survival.

Key Words: ST-segment elevation myocardial infarction, global left ventricular myocardial work efficiency, prognosis.

Clinical Perspective

Left ventricular ejection fraction (LVEF) and left ventricular global longitudinal strain (LV GLS) have prognostic value in patients with ST-segment elevation myocardial infarction (STEMI). However, LVEF and LV GLS are influenced by loading conditions. Novel speckle tracking echocardiographic indices of myocardial work integrate blood pressure measurements (afterload) with LV GLS. Global left ventricular myocardial work efficiency (GLVMWE) obtained from echocardiography-derived pressure-strain loops takes into account the afterload and reflects the LV performance. In the current study, 507 STEMI patients were retrospectively analyzed and GLVMWE were measured by transthoracic echocardiography within 48 hours of admission. Reduced GLVMWE (<86%) in patients with STEMI was independently associated with worse long-term prognosis.

INTRODUCTION

Ischemic heart disease remains as an important cause of death worldwide¹ and patients with acute myocardial infarction face a substantial risk of additional cardiovascular events, including heart failure.² Infarct size, as well as left ventricular (LV) dilation and dysfunction increase the risk of heart failure and cardiovascular mortality.³ In clinical practice, assessment of LV systolic function with left ventricular ejection fraction (LVEF) remains as a widely recognized prognostic marker.⁴ However, its limitations are well known (i.e. limited reproducibility, geometrical assumptions).⁵

Recently, two-dimensional (2D) speckle tracking echocardiography-derived LV global longitudinal strain (GLS) has demonstrated incremental value over LVEF to predict prognosis after ST-segment elevation myocardial infarction (STEMI).^{6,7} However, both LVEF and LV GLS are load-dependent parameters and their assessment are influenced by heart rate and systolic blood pressure, which have also been associated with outcomes after STEMI.⁸⁻¹⁰

The assessment of myocardial work indices based on 2D-speckle tracking echocardiography takes into consideration the loading conditions by integrating blood pressure measurements to generate a pressure-strain curve.¹¹ Specifically, global LV myocardial work efficiency (GLVMWE), which combines the measurement of constructive and wasted work, provides information on global LV performance. However, the association of this novel parameter with outcomes after STEMI has not been studied. The purpose of this study was to investigate the prognostic value of GLVMWE, obtained from pressure-strain loops with echocardiography, in patients with STEMI.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient population

A total of 507 patients with STEMI admitted to the Leiden University Medical Center (Leiden, The Netherlands) and treated with primary percutaneous coronary intervention (PCI) between August 2011 and November 2015 were identified and included in this retrospective analysis. Patients known with severe valvular heart disease and prior cardiac surgery before the index event were excluded, as well as patients without non-invasively measured blood pressure data at the time of echocardiography.

Patients were treated according to the institutional STEMI protocol¹², which provides a clinical framework for optimal guideline-based medical therapy and standardized outpatient follow-up.^{1, 13} During invasive coronary angiography, the culprit vessel was identified and multivessel disease was defined as more than one vessel with >50% luminal stenosis. Guidelines-directed medical therapy was initiated during hospitalization and echocardiography was performed within 48 hours of admission after primary PCI. Clinical and echocardiographic data were retrospectively analyzed in the departmental cardiology information system (EPD-Vision) and echocardiographic database, respectively. The Global Registry of Acute Coronary Events (GRACE) risk score¹⁴ was calculated for all population which includes the following variables: age, heart rate, systolic blood pressure, Killip class, cardiac arrest on admission, ST-segment deviation, creatinine level, and cardiac enzyme levels. For retrospective analysis of clinically acquired data, the institutional review board waived

the need for patient written informed consent.

Conventional analysis of echocardiographic data

Transthoracic echocardiography was performed in patients at rest in the left lateral decubitus position using a commercially available ultrasound system (Vivid 7, Vivid E9 or E95, GE Vingmed Ultrasound, Horten, Norway) equipped with an M5S transducer. Standard M-mode, 2-dimensional (2D), color, pulsed and continuous wave Doppler images were acquired and all images were analyzed offline using EchoPac version 203 software (GE Vingmed Ultrasound, Horten, Norway). The LVEF, LV end-diastolic (LVEDV) and end-systolic volumes (LVESV) were calculated in the 4- and 2-chamber apical views using the Simpson's biplane method.¹⁵

Analysis of LV global longitudinal strain (GLS) was performed on standard routine grey-scale images in the apical 2-, 4- and long-axis views, with a frame rate ≥ 40 frames/s. LV GLS was calculated by the software (GE Vingmed Ultrasound, Horten, Norway) as the average peak systolic strain of three apical views and presented in a 17-segment model. LV GLS are reported as absolute numbers.

Calculation of global left ventricular myocardial work efficiency

Calculation of GLVMWE was performed using a commercially available software package (EchoPac version 203 software, GE Medical Systems, Horten, Norway). As reported by Russell et al,¹¹ GLVMWE was measured from pressure-strain loop areas, which were constructed from non-invasive estimation of peak LV pressure using patients' brachial cuff blood pressure recordings (which assumes that peak systolic LV pressure is equal to peak arterial pressure) combined with speckle tracking echocardiographic strain data.

After calculating LV GLS and introducing the values of brachial blood pressure, the

opening and closing time points of the aortic and mitral valves were identified from the apical 3-chamber or parasternal long-axis views. An LV pressure-strain curve was then constructed from LV GLS data of the entire cardiac cycle, according to the duration of isovolumic relaxation and contraction, ejection and filling phases defined by timing of the aortic and mitral valve opening and closing events on 2D echocardiography as well as non-invasive blood pressure values.

LV myocardial work was calculated as the product of the rate of segmental shortening and instantaneous LV pressure. LV myocardial work is a measure of instantaneous power, which was integrated over time to obtain myocardial work as a function of time. Constructive work was defined as cardiac work performed during shortening of a myocardial segment in systole or during lengthening in isovolumic relaxation, whereas wasted work was defined as work performed by a segment during lengthening in systole, or during shortening against a closed aortic valve in isovolumic relaxation. The ratio of the constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments defines GLVMWE and is expressed as a percentage. Therefore, GLVMWE is an estimate of the mechanical performance and energy utilization of the LV that takes into consideration the loading conditions. (Figure 1).

Follow-up

Patients were followed up at the outpatient clinic according to the institutional protocol.¹² The primary end point was all-cause mortality. Mortality data after discharge was collected through municipal civil registries or by reviewing medical records. Follow-up data was available for all study patients.

Statistical analysis

Categorical data are presented as frequencies and percentages and compared with the chi-square test. Continuous data are presented as mean \pm standard deviation or median and interquartile range, as appropriate. Comparisons between patients with preserved GLVMWE versus patients with reduced GLVMWE were analyzed by the Student's t-test (if normally distributed) or the Mann-Whitney U test (if not normally distributed). To evaluate the change in hazard ratio (HR) for all-cause mortality across a range of values of GLVMWE (as a continuous variable), spline curve analysis was performed. A cut-off value of GLVMWE to define reduced and preserved GLVMWE was derived from the spline curve (i.e. when the HR of the lower limit of the 95% confidence interval was ≥ 1). The cumulative event-free survival was calculated based on Kaplan–Meier analysis and compared between groups with a log-rank test. The association of clinical and echocardiographic variables (including GLVMWE) with all-cause mortality were tested using Cox proportional hazard regression analysis. The HR and 95% confidence intervals were calculated. The GRACE risk score¹⁴ was utilized to incorporate all important confounding variables into the multivariable analyses while avoiding model overfitting. To assess the incremental advantage of GLVMWE over baseline clinical characteristics, LVEF and LV GLS for the risk of all-cause mortality the change in chi-square was assessed. The interobserver and intraobserver variability of GLVMWE was assessed in 20 randomly selected patients and the intraclass correlation coefficients were calculated. All statistical analyses were performed with SPSS software version 25.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) and were two-sided. A p-value <0.05 was considered statistically significant.

RESULTS

Study population and clinical characteristics

This retrospective study included 507 patients (384 males (76%), mean age 61 ± 11 years) with STEMI (Table 1). The patient sample was divided according to the cut-off value of GLVMWE associated with an excess of mortality as assessed with spline curve analysis. After an initial plateau region until GLVMWE dropped below 90%, there was a substantial increase in HR for values of GLVMWE $< 86\%$. In addition, another plateau region was observed with values below 80%, where a further reduction in GLVMWE did not appear to substantially increase the risk of all-cause mortality (Figure 2). Based on this analysis, a GLVMWE value $< 86\%$ was used to define a reduced GLVMWE and to dichotomize the population. The clinical characteristics of patients divided according to the presence of preserved ($\geq 86\%$) vs. reduced ($< 86\%$) GLVMWE are summarized in Table 1. Reduced GLVMWE was observed in 126 patients (25%), with a median value of 81% (interquartile range (IQR) 77-83%). Patients with reduced GLVMWE were significantly older, had a higher heart rate, higher GRACE risk score, the left anterior descending coronary artery was the most frequently involved culprit vessel. The proportion of women was higher in the group of reduced GLVMWE versus the group with preserved GLVMWE (31% vs. 22%, respectively). In addition, patients with reduced GLVMWE showed more myocardial damage based on significantly higher values of creatine phosphokinase and troponin T in comparison with patients with preserved GLVMWE.

The echocardiographic characteristics of the study population are shown in Table 2. In the overall population, the mean LVEF was $52\pm 10\%$ with a mean LV GLS of $15\pm 4\%$. Patients with reduced GLVMWE had significantly larger LVESV and LVEDV, significantly lower LVEF and more impaired LV GLS as compared to patients with

preserved GLVMWE.

Survival analysis

After a median follow-up of 80 months (IQR 67-97 months), 40 (8%) patients died. The Kaplan–Meier curves for all-cause mortality are shown in Figure 3. Patients with reduced GLVMWE showed higher cumulative event rates at 80 months (17.5% vs. 4.7%; log-rank $p < 0.001$) versus patients with preserved GLVMWE. The univariable and multivariable Cox regression analyses were constructed with variables known to be associated with outcomes in STEMI patients (Table 3). In univariable analysis age, Killip class \geq II, heart rate, diabetes mellitus, higher creatinine levels, higher peak troponin T levels, higher GRACE risk score, lower LVEF, impaired LV GLS and GLVMWE $< 86\%$ were significantly associated with all-cause mortality. On multivariable Cox regression analysis, higher GRACE risk score, diabetes mellitus and GLVMWE $< 86\%$ were independently associated with all-cause mortality. Furthermore, GLVMWE $< 86\%$ demonstrated incremental prognostic value over baseline clinical characteristics and LVEF and LV GLS (Figure 4). The increment in chi-squared was higher when adding GLVMWE than when adding LVGLS (Figure 4). When performing the Cox regression analyses with GLVMWE as continuous variable, more impaired GLVMWE was associated with worse outcomes (Supplemental material. Table I). Due to the limited number of events during follow-up, other multivariable models were constructed including a maximum of 4 variables each time (Supplemental material. Table II). In all the models, a GLVMWE $< 86\%$ was significantly associated with all-cause mortality.

Reproducibility

Measurements of GLVMWE showed excellent intraobserver [ICC 0.904 (95% CI: 0.777-0.961; $p < 0.001$)] and interobserver agreement [ICC 0.916 (95% CI: 0.801-

0.966); $p < 0.001$]).

DISCUSSION

The main findings of the present study can be summarized as follows: STEMI patients with reduced GLVMWE (<86%) showed more myocardial damage with higher values of creatine phosphokinase and troponin T, larger LVESV and LVEDV, and a significantly lower LVEF with more impaired LV GLS as compared to their counterparts. In addition, reduced GLVMWE was associated with worse long-term prognosis after STEMI.

Prognostic implications of LVEF and LV GLS after acute myocardial infarction

Current guidelines recommend routine echocardiography before discharge in all STEMI patients to assess LVEF and diastolic function, as well as other parameters that may influence outcome such as wall motion score index and valvular heart disease¹. Recent studies reported that LV GLS measured with echocardiography¹⁶ and cardiac magnetic resonance imaging¹⁷ predicts cardiovascular death after myocardial infarction and has incremental prognostic value over LVEF¹⁸. However, similar to LVEF, LV GLS is also influenced (although to a lesser extent) by loading conditions – especially afterload¹⁹. Non-invasive assessment of GLVMWE compared to standard parameters of LV function (i.e. LVEF, LV GLS), integrates LV GLS, afterload and isovolumic relaxation phase to provide a more comprehensive measure of LV myocardial performance. Moreover, it correlates with myocardial glucose metabolism assessed on ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography, providing an estimate of LV myocardial energetics¹¹. The relation between GLVMWE measurement and STEMI was previously reported on by El Mahdiui et al²⁰. The

authors found that STEMI patients showed lower values of GLVMWE in comparison with healthy subjects and patients with cardiovascular risk factors. In the current study, which included exclusively STEMI patients, those with reduced GLVMWE (<86%) showed evidence of more cardiac damage than STEMI patients with preserved GLVMWE ($\geq 86\%$). Indeed, after STEMI, ischemia induces changes in myocardial metabolism, reducing adenosine triphosphate (ATP) formation²¹, leading to LV contractile dysfunction and reduced values of GLVMWE.

Prognostic implications of GLVMWE after STEMI

Myocardial efficiency is related to the capacity of the heart to generate effective work based on hemodynamic parameters, oxygen consumption and myocardial metabolism²². At this moment, the prognostic implications of GLVMWE in patients with STEMI have not been explored. However, previous studies have related GLVMWE to prognosis in different populations. Kim et al reported the prognostic value of invasive myocardial efficiency in 47 patients with dilated cardiomyopathy and demonstrated that patients with invasive myocardial efficiency below 11% showed worse prognosis²³. Van der Bijl et al analyzed the prognostic role of GLVMWE in 153 patients with heart failure with indication for cardiac resynchronization therapy (CRT)²⁴. The authors demonstrated that a GLVMWE <75% measured before CRT implantation was associated with a better long-term outcome. The present study provides further evidence on the prognostic implications of GLVMWE in a large cohort of STEMI patients, showing that patients with reduced GLVMWE had worse prognosis at long-term follow-up. In addition, GLVMWE demonstrated incremental advantage over LVEF and the change in chi-squared of the model was higher when adding GLVMWE than when adding LV GLS. Interestingly, higher values of GLVMWE were associated with better outcome, independent of other clinical parameters (Supplemental material.

Table I).

Study limitations

This was a retrospective single-center study, and prospective validation is needed. Moreover, the GLVMWE was evaluated in a registry of STEMI patients and the clinical value of this index in other patient populations needs to be evaluated.

CONCLUSION

A reduced GLVMWE measured on transthoracic echocardiography within 48 hours of admission is associated with worse long-term survival in STEMI patients.

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DISCLOSURES

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SUPPLEMENTAL MATERIALS

Supplemental tables I-II

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Table 1. Clinical characteristics

Variable	All patients	Preserved	Reduced	p-value
	(n=507)	GLVMWE (≥ 86%) (n=381)	GLVMWE (< 86%) (n=126)	
Age (yrs)	61±11	60±11	64±12	<0.001
Male, n(%)	384 (76)	297 (78)	87 (69)	0.043
Killip classification I, n(%)	477 (94)	360 (94)	117 (93)	0.501
Sinus rhythm, n(%)	502 (99)	378 (99)	124 (98)	0.431
Heart Rate (bpm)	73±12	71±12	78±13	<0.001
LBBB, n(%)	3 (0.6)	1 (0.3)	2 (1.6)	0.093
SBP (mmHg)	122±18	122±18	124±21	0.332
DBP (mmHg)	75±12	74±12	77±13	0.049
Symptom onset to balloon time (min)	157 (106-255)	152 (104-233)	183 (114-334)	0.013
Peak CK value at baseline (U/L)	1168 (562-2317)	1029 (498-1880)	2171 (950-3567)	<0.001
Peak Troponin T at baseline (µg/L)	3.01 (1.36-6.34)	2.54 (1.12-5.17)	5.71 (2.55-9.77)	<0.001

Creatinine level ($\mu\text{mol/L}$)	76 (67-89)	77 (67-89)	74 (63-87)	0.164
eGFR (ml/min/1.73m^2)	90 (76-100)	90 (77-100)	90 (72-97)	0.322
GRACE risk score (points)	113 \pm 24	111 \pm 22	120 \pm 27	0.001
Hypertension, n(%)	190 (38)	129 (34)	61 (49)	0.003
Diabetes mellitus, n(%)	31 (6)	19 (5)	12 (10)	0.067
Dyslipidemia, n(%)	89 (18)	64 (17)	25 (20)	0.466
Smoker, n(%)	224 (45)	174 (47)	50 (40)	0.203
Family history of CAD, n(%)	215 (44)	165 (45)	50 (41)	0.416
Previous myocardial infarction, n(%)	15 (3)	10 (3)	5 (4)	0.440
LAD STEMI, n(%)	236 (47)	133 (35)	103 (82)	<0.001
Other STEMI locations, n(%)	271 (53)	248 (65)	23 (18)	<0.001
Final TIMI flow ≤ 2 , n(%)	24 (5)	18 (5)	6 (5)	0.986
Multivessel disease, n(%)	276 (54)	209 (55)	67 (53)	0.743
Aspirin, n(%)	506 (99)	381 (100)	125 (99)	0.082
P2Y12 inhibitors, n(%)	507 (100)	381 (100)	126 (100)	1.00
β -Blocker, n(%)	485 (96)	365 (96)	120 (95)	0.788

Statin, n(%)	506 (99)	381 (100)	125 (99)	0.082
ACEI or ARB, n(%)	495 (98)	371 (97)	124 (98)	0.507
Nitrates, n(%)	419 (83)	317 (83)	102 (81)	0.563

Values are mean \pm SD or median (IQR). ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin receptor blocker; CAD: Coronary artery disease; CK: Creatine phosphokinase; DBP: Diastolic blood pressure; eGFR: estimated glomerular filtration rate; GLVMWE: Global left ventricular myocardial work efficiency; GRACE: Global registry of acute coronary events; LAD: Left anterior descending artery; LBBB: Left bundle branch block; SBP: Systolic blood pressure; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in myocardial infarction.

Table 2. Echocardiographic characteristics of the study population at baseline

Variable	All	Preserved	Reduced	p-value
	patients (n=507)	GLVMWE (\geq 86%) (n=381)	GLVMWE (< 86%) (n=126)	
Left ventricular end-systolic volume (ml)	43 (32-57)	40 (30-52)	51 (41-68)	<0.001
Left ventricular end-diastolic volume (ml)	89 (71-111)	88 (70-107)	95 (78-122)	0.003
Left ventricular ejection fraction (%)	52 \pm 10	55 \pm 9	45 \pm 9	<0.001
Moderate mitral regurgitation, n(%)	32 (6)	22 (6)	10 (8)	0.379
Left ventricular global longitudinal strain (%)	15 \pm 4	16 \pm 3	10 \pm 3	<0.001
GLVMWE (%)	92 (86-95)	94 (91-96)	81 (77-83)	<0.001

Values are mean \pm SD or median (IQR). GLVMWE: Global left ventricular myocardial work efficiency. Left ventricular global longitudinal strain is presented as positive value.

Table 3. Univariable and multivariable Cox regression analysis for all-cause mortality

Variable	Univariable analysis			Multivariable analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Age, yrs	1.067	1.036-1.100	<0.001			
Male gender	0.838	0.419-1.678	0.618			
Killip class \geq II	3.229	1.352-7.715	0.008			
Heart rate, bpm	1.025	1.002-1.049	0.035			
Systolic blood pressure, mmHg	0.998	0.980-1.015	0.778			
Symptom onset to balloon time, min	1.000	1.000-1.001	0.376			
Creatine phosphokinase, U/l	1.000	1.000-1.000	0.312			
Troponin T, μ g/l	1.050	1.009-1.093	0.018			
Creatinine level, μ mol/L	1.012	1.006-1.019	<0.001			

Diabetes mellitus	3.509	1.551-7.935	0.003	3.233	1.424-7.340	0.005
Left anterior descending as culprit artery	0.964	0.517-1.797	0.908			
Multivessel disease	1.586	0.828-3.036	0.164			
GRACE risk score, (each 1 point increment)	1.031	1.019-1.043	<0.001	1.029	1.016-1.042	<0.001
LVEF, (each 1% increment)	0.951	0.922-0.981	0.002			
LV GLS, (each 1% increment)	0.870	0.804-0.942	0.001			
Baseline, GLVMWE <86%	4.109	2.202-7.665	<0.001	3.167	1.679-5.972	<0.001

CI: Confidence interval; GLMWE: Global left ventricular myocardial work efficiency; GRACE: Global registry of acute coronary events; HR: Hazard ratio; LVEF: Left ventricular ejection fraction.; LV GLS: Left ventricular global longitudinal strain, and is presented as positive value. Therefore, more positive value, better function and better outcome.

Figure Legends

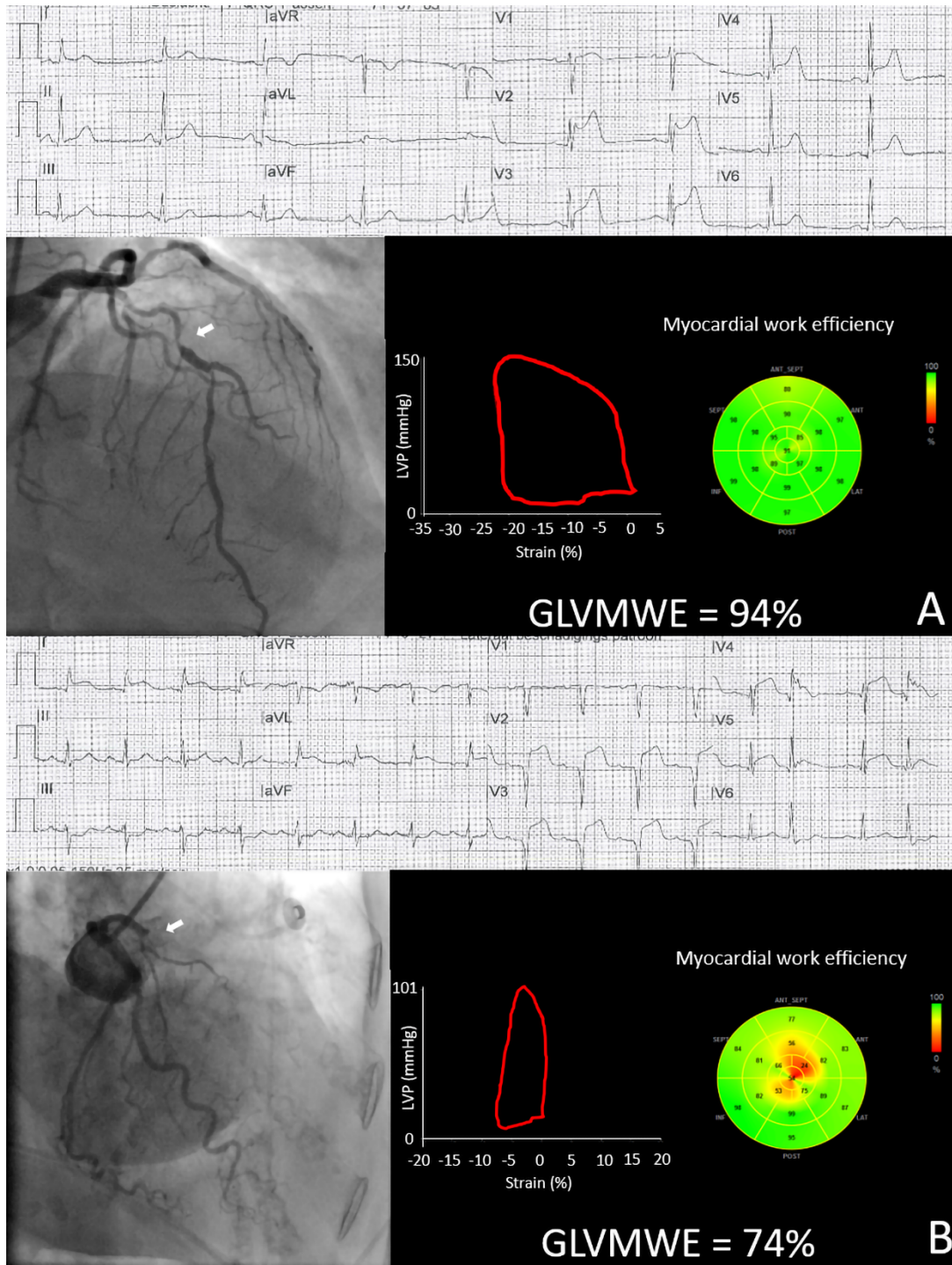


Figure
1.

Calculation of global LV myocardial work efficiency. Electrocardiogram showing anterior STEMI, coronary angiography showing the LAD culprit vessel (white arrow) and LV myocardial work efficiency bull's-eye plots of STEMI patients with preserved GLVMWE ($\geq 86\%$) (panel A) and reduced GLVMWE ($< 86\%$) (panel B). Preserved

segmental values of LV myocardial work efficiency are presented in green and reduced segmental values of LV myocardial work efficiency are presented in yellow. Segmental values of LV myocardial work efficiency are expressed as a percentage. GLVMWE: global left ventricular myocardial work efficiency. LAD: left anterior descending coronary artery. LV: left ventricular. STEMI: ST-segment elevation myocardial infarction.

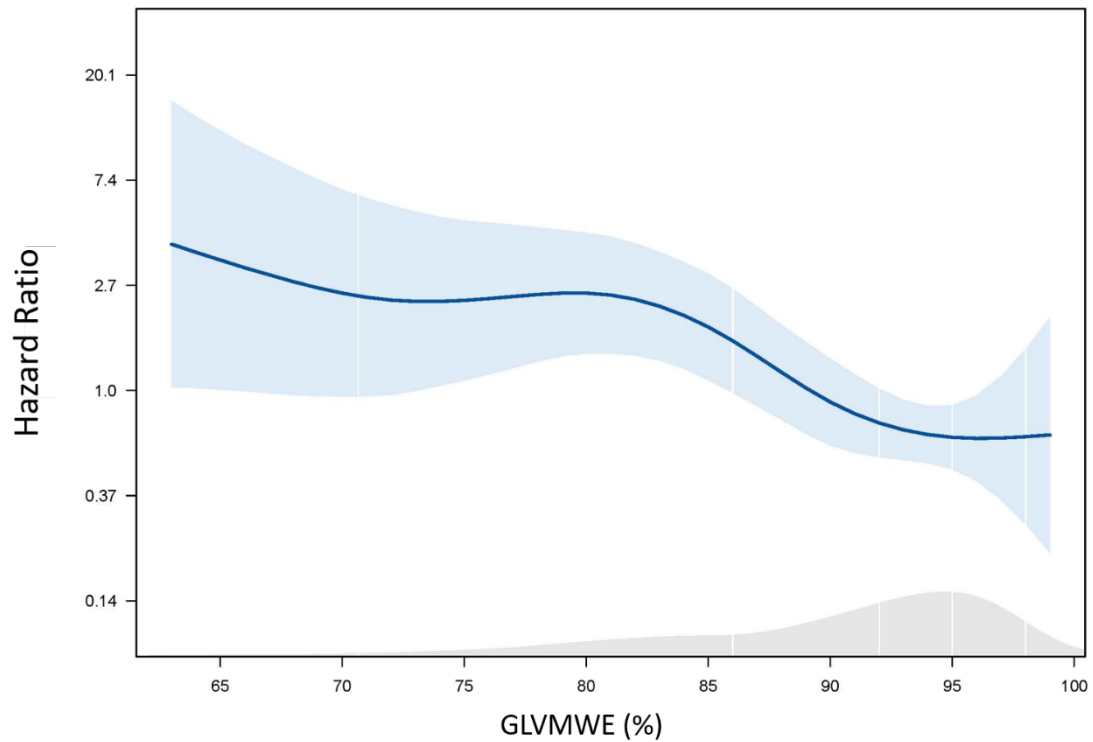
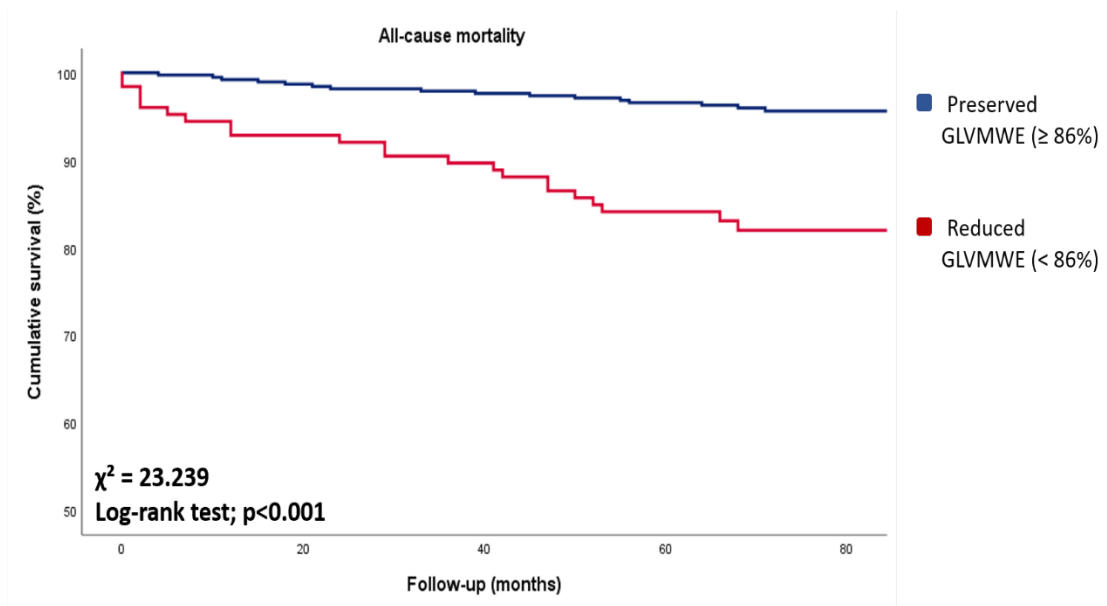


Figure 2. Spline curve for baseline GLVMWE vs. hazard ratio of all-cause mortality in patients after STEMI. The spline curve demonstrates the hazard ratio change for all-cause mortality across a range of values of GLVMWE. The density plot beneath the curve demonstrates the distribution of the study population according to the values of GLVMWE. GLVMWE: global left ventricular myocardial work efficiency. STEMI: ST-segment elevation myocardial infarction.



Number of patients at risk

Preserved GLVMWE (≥ 86%)	381	376	371	358	208
Reduced GLVMWE (< 86%)	126	117	113	102	57

Figure 3. Survival

analysis. The Kaplan-Meier curves depicting time to cumulative survival in ST-segment elevation myocardial infarction patients. Data are shown according to those with preserved and reduced GLVMWE. GLVMWE: global left ventricular myocardial work efficiency.

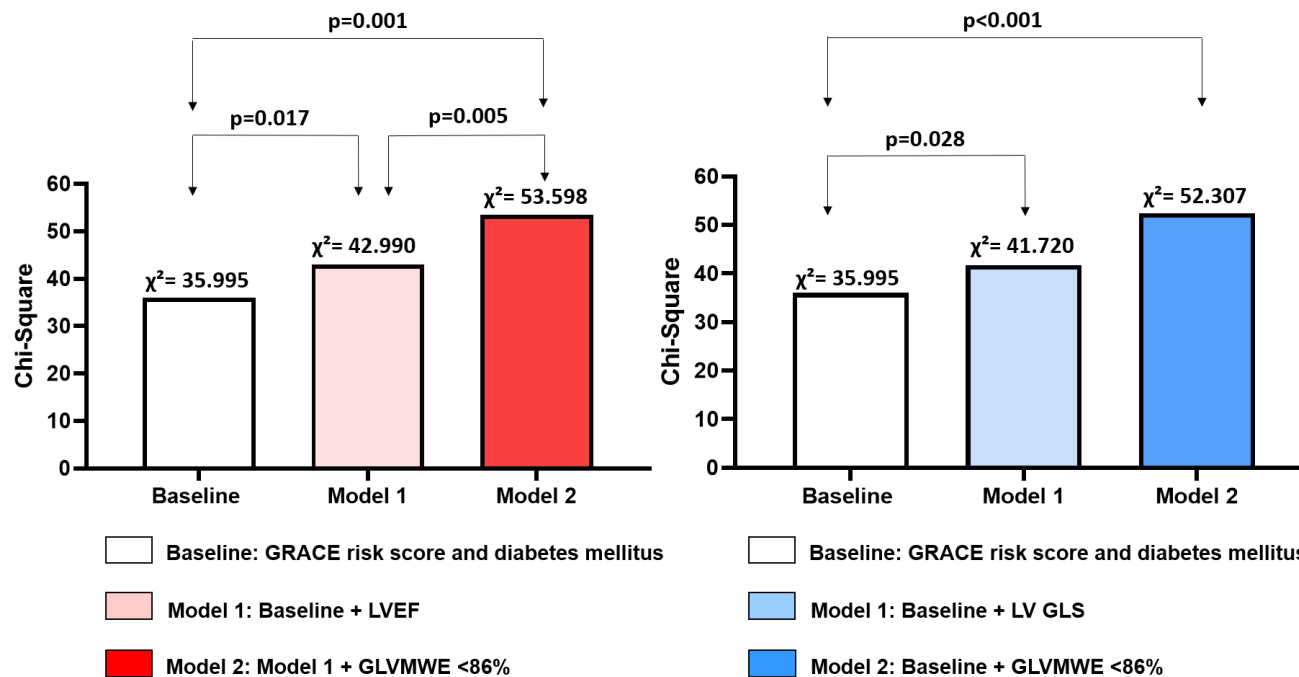


Figure 4. Incremental prognostic value of GLVMWE in patients with ST-segment elevation myocardial infarction. The bar graphs show the χ^2 value for the three models associated with all-cause mortality. The baseline model includes GRACE risk score and diabetes mellitus. The addition of GLVMWE provides incremental prognostic information over the baseline model and models incorporating LVEF and LV GLS. GLVMWE: global left ventricular myocardial work efficiency. GRACE: global registry of acute coronary events. LVEF: left ventricular ejection fraction. LV GLS: left ventricular global longitudinal strain.

Supplemental material:

Table I: Univariable and multivariable Cox regression analysis for all-cause mortality

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GRACE risk score, (each 1 point increment)	1.031	1.019-1.043	<0.001	1.030	1.016-1.043	<0.001
LVEF, (each 1% increment)	0.951	0.922-0.981	0.002			
LV GLS, (each 1% increment)	0.870	0.804-0.942	0.001			
GLVMWE, (each 1% increment)	0.940	0.911-0.970	<0.001	0.955	0.924-0.987	0.006

GLVMWE is included as continuous variable. CI: Confidence interval; GLMWE: Global left ventricular myocardial work efficiency; HR: Hazard ratio; LVEF: Left ventricular ejection fraction; LV GLS: Left ventricular global longitudinal strain, and is presented as positive value. Therefore, more positive value, better function and better outcome.

Table II: Multivariable Cox regression models for all-cause mortality

Variable	Multivariable analysis adjusting for GRACE, diabetes, and LVEF		Multivariable analysis adjusting for age, creatinine and LVEF		Multivariable analysis adjusting for age, peak cardiac troponin and diabetes		Multivariable analysis adjusting for Killip class≥II, peak cardiac troponin and LVEF		Multivariable analysis adjusting for creatinine, diabetes and LVEF	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Baseline, GLVMWE <86%	2.729 (1.354-5.502)	0.005	2.960 (1.461-5.995)	0.003	3.077(1.612-5.871)	0.001	3.396(1.669-6.911)	0.001	3.474(1.714-7.040)	0.001

CI: Confidence interval; GRACE: Global registry of acute coronary events; GLMWE: Global left ventricular myocardial work

efficiency; HR: Hazard ratio; LVEF: Left ventricular ejection fraction.