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Non-Invasive Cardiac Laboratory, Brigham´s and Women's Hospital, Boston, MA

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Tese de Doutorado

Insuficiência Cardíaca com Fração de Ejeção Preservada: análise da função de ventrículo esquerdo e de átrio esquerdo baseada em *strain* miocárdico.

Aluna: Ângela Barreto Santiago Santos

Orientador Brasileiro: Luis Eduardo P. Rohde

Orientador Estrangeiro: Scott D. Solomon

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Índice

Abreviaturas

IC=Insuficiência Cardíaca

ICFER= Insuficiência Cardíaca com Fração de Ejeção Reduzida

ICFEP= Insuficiência Cardíaca com Fração de Ejeção Preservada

FE=Fração de Ejeção

VE=Ventrículo Esquerdo

AE =Átrio Esquerdo

NT-proBNP = N-terminal do peptídeo natriurético tipo B

Introdução

Insuficiência cardiaca (IC) é uma síndrome clínica caracterizada por anormalidade na estrututa e funcionamento cardíaco que resulta em aumento da pressão de enchimento do ventrículo esquerdo ou prejuízo da ejeção de sangue ao suprir as necessidade metabólicas teciduais corporais. A caracterização da fração de ejeção (FE) do ventrículo esquerdo (VE) é parte fundamental na classificação clássica de IC, permitindo a divisão dos paciente em dois grandes grupos com características demográficas, comorbidades, prognóstico e resposta terapêutica diferentes: IC com fração de ejeção reduzida (ICFER) e IC com fração de ejeção preservada (ICFEP). [1,2] Além disso, é baseado na FE que a maioria dos ensaios clínicos em IC selecionam seus pacientes. No entanto, o ponto de corte da FE para definição de ICFEP é variável dentre os ensaios clínicos (CHARM-Preserved Trial[3]: FE >40%, DIG-PEF[4], I-Preserve[5], PARAMOUNT[6] and TOPCAT[7]: FE>45%; ALDO-DHF[8]: FE >55%). A classificação dos grupos de IC baseado na FE, de acordo com o mais recente guideline americano, tem como ponto de corte FE ≤40% para ICFER e FE>40% para ICFEP, sendo o grupo de paciente com FE entre 41 e 49%, considerado um grupo intermediário de ICFEP.

IC com fração de ejeção preservada

ICFEP corresponde a aproximademente metade de todos os casos de IC. [9-12] A prevalência é maior com o avançar da idade, em mulheres, pacientes com história de hipertensão arterial e fibrilação atrial e com cardiopatia não isquêmica. ICFEP constitui-se em um problema de saúde pública com prevalência e proporção de hospitalizações em ascensão, acompanhando o

aumento da prevalência das comorbidades relacionadas a essa síndrome e o envelhecimento das populações.[13] Estudo recente envolvendo um total de 110.621 pacientes, mostrou que 50% dos pacientes admitidos em 275 diferentes hospitais americanos tinham diagnóstico de ICFEP, sendo que destes pacientes, 36% tinham fração de ejeção $\geq$50% e 14% tinham fração de ejeção entre 40 e 50%. Nesse estudo, no decorrer de 5 anos (2005 a 2010), houve um aumento de 33% para 39% ($p<0,0001$) na proporção de pacientes hospitalizados por ICFEP, com concomitante redução na proporção de hospitalizações por ICFER.[14]

Enquanto os critérios diagnóstico para ICFER são bem definidos, o diagnóstico de ICFEP é uma desafio, envolvendo primeiramente a exclusão de uma variedade de causas não cardíacas para os sintomas de IC. Enquanto a diretriz americana apenas cita critérios para definição de ICFEP (sinais ou sintomas de IC, evidência de FE de VE normal e evidência de disfunção diastólica)[2], a diretriz européia de IC determina quatro critérios diagnósticos que devem ser preenchidos para o diagnóticos de ICFEP: sintomas típicos de IC; sinais típicos de IC; FE de VE normal ou levemente reduzida com VE não dilatado; e alteração estrutural cardíaca (hipertrofia de VE ou dilatação de átrio esquerdo) e/ou disfunção diastólica.[1] A diretriz brasileira sugere um fluxograma para melhor diagnótico de IC em seus dois grandes grupos, que envolve anamnese, exame físico e exames complementares , onde é destacado o papel do BNP ou NT-proBNP na definição objetiva de congestão.[15]

Apesar do pobre prognóstico associado a ICFEP, dados de uma metanálise contemporânea mostraram que o prognóstico de pacientes com ICFEP ainda é melhor do que em pacientes com ICFER (ICFEP 121 mortes por 1.000 pacientes-anos versus ICFER 141 mortes por 1.000 pacientes-ano, o que representa um risco de morte 32% menor em ICFEP comparado a ICFER em 3 anos). Essa metanálise ainda demonstrou que o risco de morte dos pacientes

analisados não aumentava de forma significativa em todo grupo de pacientes com FE acima de 40%, enquanto pacientes com FE <40%,apresentavam maior risco de morte, reforçando o ponto de corte da FE acima de 40% nos ensaios clínicos farmacológicos de ICFER.[16] Deve-se ressaltar que similarmente ao que ocorre em paciente com ICFER, o risco de morte em ICFEP aumenta consideralmente após hospitalização por IC.[17] O predomínio de mortes por causa cardiovascular versus não-cardiovascular associado a ICFEP é variável conforme o tipo do estudo analisado: estudos baseados em coortes da comunidade mostram maior proporção de mortes por causa não-cardiovascular enquanto ensaios clínicos mostram maior predomínio de mortes por causa cardiovascular, refletindo o perfil mais saudável dos pacientes selecionados para os ensaios clínicos.[18]

Até o presente momento, não há nenhuma terapia com comprovado efeito na redução de mortalidade e hospitalizações atribuídas a ICFEP, apesar das inúmeras intervenções terapêuticas com comprovado benefício sobre sobrevida e hospitalizações dos pacientes com ICFER.[19] Estudos recentes mostraram melhora de desfechos intermediários atribuídos ao inibidor do receptor da angiotensiona neprilisina (diminuição de peptídeos natriuréticos e volume do átrio esquerdo)[6] e a espironolactona (melhora da função diastólica e hipertrofia de VE)[8] embora pelo menos no caso da espironolactona, esse resultado não se reproduza em redução de mortalidade e hospitalizações como desfecho primário em estudo clínico posterior (TOPCAT).[7] A semelhança de estudo prévio[3], o TOPCAT mostrou apenas redução de hospitalização por IC quando esse componente foi avaliado isoladamente. Assim, o manejo para ICFEP ainda é limitado ao manejo das comorbidades associadas e diuréticos.

Um dos poucos consensos que há na síndrome da ICFEP é que está é uma síndorme heterogênea, onde os pacientes possuem comorbidades em comum, mas a maioria dos casos não

tem uma etiologia específica primária. A melhor compreensão dos mecanismos fisopatógicos associados a ICFEP podem ajudar na identificação de melhores alvos terapêuticos.

Mecanismos fisiopatológicos

O mecanismo fisiopatológico da ICFEP é complexo e ainda não completamente entendido. Tradicionalmente, essa síndrome tem sido atribuída primariamente a anormalidades da função diastólica, por isso a denominação frequentemente utilizada de IC diastólica. Disfunção diastólica inclui prolongamento do relaxamento ativo e aumento da complascência passiva do VE, baseado em estudos que usaram mensurações invasivas desses parâmetros.[20,21] A alteração na função diastólica resultaria em um ineficiente esvaziamento do átrio esquerdo (AE) e aumento das pressões de enchimento do VE, com diminuição da capacidade do miocárdio em suprir o aumento das demandas metabólicas teciduais durante o exercício, aumento da pressão pulmonar e sinais e sintomas de retenção de líquidos. Na ausência de patologias envolvendo endocárdio e pericárdio, a alteração da função diastólica tem sido atribuída a um aumento da rigidez miocárdica, seja por alteração dos cardiomiócitos e/ou da matriz extracelular.[22] Evidências atuais sugerem que o remodelamento miocárdico observado na ICFEP está relacionado a presença de um estado inflamatório nesses pacientes, decorrente a comorbidades prevalentes nessa síndrome, como hipertensão, obesidade, diabetes mellitus, doença obstrutiva crônica.[23] A ativação do endotélio microvascular coronariano, induzida por esse estado inflamatório, resultaria na produção de espécies reativas de oxigênio e consequente redução da bio-disponibilidade de óxido nítrico, guanosina monofosfato cíclica (GMPc) e proteína quinase G.[24] Essa sequência de eventos estimularia hipertrofia de cardiomiócitos (via alterações da proteína titina), fibrose interticial e consequente aumento rigidez miocárdica. Na ICFEP, essa

sequência de eventos não consegue ser atenuada pela ação do peptídeo atrial natriurético (BNP)- que atuaria normalizando os componentes em falência decorrente do estresse oxidativo, especialmente GMPc- já que as moléculas de BNP encontram-se reduzidas na sua forma biologicamente ativa e com maior resistência ao seu efeito nessa síndrome.[6,25]

Recentemente, outros mecanismos fisiopatológicos, além da disfunção diastólica, têm sido identificados como tendo um papel importante no desenvolvimento da ICFEP: aumento da rigidez vascular sistêmica e pulmonar, anormalidades do acomplamento ventrículo-arterial e atenuação da vasodilatação sistêmica durante o exercício; prejuízo da reserva funcional sistólica e diastólica do VE, seja por anormalidades no retorno venoso, na vasodilatação periférica, no aumento da contratilidade miocárdica ou da frequência cardíaca; incompetência cronotrópica, prejuízo na utilização periférica de oxigênio.[22,26]

Adicionalmente, evidências iniciais apontam para a presença de alteração na função sistólica do VE presente na ICFEP[27,28], concomitante a FE preservada, como também a presença de dissincronia mecânica e sua associação a ineficiência do processo contração e relaxamento miocárdico.[29,30] Ainda, alterações na estrutura e funcionamento de outras cavidades cardíacas além do VE, como o AE, podem contribuir para a síndrome da ICFEP.[31]

Disfunção sistólica e ICFEP

Por definição, a função sistólica aferida pela FE do VE encontra-se dentro dos limites da normalidade nos pacientes com ICFEP. No entanto, apesar dessa variável ser a mais comumente usada para avaliar a contratilidade miocárdica na prática clínica, a FE do VE é altamente dependente das condições de pré-carga e pós-carga cardíaca e não detecta alterações sutis da

contratilidade miocárdica.[32,33] Assim, para melhor compreensão da contratilidade cardíaca nesses pacientes, faz-se necessário a utilização de outros parâmetros.

Estudos iniciais utilizando parâmetros como encurtamento médio-parietal do VE[34] e deslocamento do plano átrio-ventricular durante a sístole ventricular[35] revelaram que pelo menos uma parte (25 a 30%) dos pacientes com ICFEP mostravam disfunção contrátil. Quando a função contrátil foi avaliada por Doppler tecidual, a anormalidade na função sistólica tornava-se evidente nos pacientes com ICFEP e apresentava valores intermediários entre pacientes com ICFER e controles saudáveis ou pacientes assintomáticos com disfunção diastólica.[27,36]

Mais recentemente, o surgimento da técnica do *speckle-tracking* através da análise de imagens ecocardiográficas no modo bi-dimensional tem permitido a avaliação da função contrátil do VE independente do ângulo de incidência da aquisição da imagem, de forma mais acurada que o Doppler tecidual e não limitado a avaliação da função contrátil no plano longitudinal cardíaco.[37] Com essa metodologia, é possível avaliar as fibras miocárdicas em seus eixos de orientação específicos (fibras subendocardíacas e sua deformação longitudinal e fibras subepicárdicas e sua deformação circunferencial e radial). Estudos menores, unicêntricos e envolvendo um pequeno número de pacientes mostraram a presença de disfunção sistólica usando *speckle tracking* em pacientes com ICFEP.[38,39] Entretanto, ainda não está claramente definido a frequência e magnitude da disfunção sistólica associada à ICFEP.

Dissincronia cardíaca e ICFEP

Em condições de normalidade, a contração ventricular ocorre de forma altamente coordenada, com ativação do endocárdio para o epicárdio e do ápice para a base, de maneira quase coincidente em todas as regiões do ventrículo esquerdo.[40] A interferência nesse processo

de ativação e contração do ventrículo esquerdo leva a dissincronia cardíaca resultando na ineficiência mecânica miocárdica. Além disso, a heterogeneidade temporal da função sistólica pode interferir na relação coordenada entre encurtamento sistólico e posterior estiramento diastólico das fibras miocárdicas.[41] Um estudo com pacientes com ICFER estáveis, comparou a função diastólica daqueles com dissincronia significativa (bloqueio de ramo esquerdo), com aqueles sem dissincronia aparente. Aqueles pacientes com dissincronia cardíaca, revelaram maior frequência de disfunção diastólica grave, pressão de enchimento de VE mais elevada e maiores níveis séricos de NT-proBNP.[42]

Na ICFER, a presença de dissincronia cardíaca é um preditor independente para eventos adversos cardiovasculares, incluindo mortalidade[43] e a terapia de ressincronização melhora a sobrevida nesse pacientes.[44] Evidências iniciais sugerem a presença de dissincronia cardíaca também na ICFEP. Em 2010, Phan e colaboradores mostraram que pacientes com ICFEP (n=38) possuiam maior dissincronia longitudinal que controles saudáveis com idade e sexo similares a pacientes com ICFEP, mesmo naqueles pacientes com QRS <120ms (sem aparente dissincronia elétrica).[45] Mais recentemente, outro grupo mostrou mostrou maior dissincronia em pacientes com ICFEP (n=85) ainda que comparados a indivíduos assintomáticos com disfunção diastólica do VE. Nesse estudo, a presença de dissincronia cardíaca foi associada a prejuízo na função sistólica longitudinal do VE (aferida por *speckle tracking*), assim como a disfunção diastólica.[46] Entretando, é necessária uma maior evidência de dissincronia de VE em ICFEP, usando uma amostra maior e bem caracterizada de pacientes com ICFEP, de preferência vinda de múltiplos centros.

Disfunção do átrio esquerdo e ICFEP

A maioria dos pacientes om ICFEP apresenta aumento do tamanho do átrio esquerdo (AE), primariamente como um marcador de disfunção diastólica e reflexo do aumento prolongado da pressão de enchimento do VE. A dilatação do AE está associada a aumento de risco para morbidade e mortalidade cardiovascular.[47,48] Entretando, dois grandes ensaios clínicos (CHARM-Preserved and I-Preserve) mostraram que em torno de um terço dos pacientes com ICFEP não apresentam qualquer alteração do tamanho do AE.[49,50] Se esses pacientes sem alteração estrutural do átrio esquerdo, já apresentam alguma alteração da função do átrio esquerdo ainda é uma lacuna do conhecimento a ser preenchido.

O AE possue três funções diferentes no ciclo cardíaco: durante a sistóle do VE, o AE atua como um reservatório de fluxo cardíaco; durante a diástole do VE, após a abertura da válvula mitral , o AE atua inicialmente como uma cavidade de condução do fluxo cardíaco para o VE, e, no fim dessa fase, o AE atua como uma bomba, impulsinando o fluxo cardíaco de forma ativa para o VE.

Estão surgindo evidências que o prejuízo da função do AE seja mais um fator a contribuir na fisiopatologia da ICFEP. Melenovsky e colaboradores mostraram, numa amostra pequena de ICFEP (n=37), que além de alterações estruturais do AE, a disfunção do AE em suas três fases pôde diferenciar pacientes com ICFEP de hipertensos assintomáticos com hipertrofia de VE, talvez sendo esse um fator que contribui para a transição de um estado assintomático de alteração estrutural de VE para outro de evidente IC.[48] Dois anos após, outro grupo de pesquisadores usando uma metodologia mais acurada para medir função do AE (*strain e strain rate*) estudaram a fase de reservatório e função de bomba do AE e mostraram que a disfunção na fase de reservatório do AE conseguia diferenciar indivíduos com ICFEP (n=20) daqueles com disfunção

diastólica assintomática (n=19), o mesmo não acontecendo pela análise estrutural do AE.[31] Mais recentemente, Morris e colaboradores, usando metodologia semelhante ao estudo anterior para estudar a função do AE (função reservatório e função de bomba do AE), compararam uma amostra maior de pacientes com ICFEP (n=119) e indivíduos assintomáticos com disfunção diastólica (n=301). Nesse estudo, a disfunção do AE nessas duas fases foi novamente reafirmada no grupo com ICFEP, concomitante a alteração estrutural do AE.[51]

Novos estudos tornam-se necessários para ampliar o conhecimento da função do AE na ICFEP em suas três fases, principalmente nos subgrupos de pacientes sem alteração estrutural do AE ou história de fibrilação atrial.

Hipóteses

1.A sincronia ventricular esquerda está alterada em pacientes com ICFEP, sendo associada a disfunção diastólica e sistólica.

2.A função sistólica ventricular esquerda está alterada em pacientes com ICFEP, quando aferida por *strain* miocárdico, sendo associada a níveis elevados do fragmento NT-proBNP independente da função diastólica.

3.A função do átrio esquerdo está alterada em pacientes com ICFEP, mesmo naqueles sem aumento do AE ou história de fibrilação atrial.

Objetivos

1.Comparar a sincronia cardíaca em pacientes com ICFEP e controles saudáveis e avaliar se a dissincronia cardíaca presente na ICFEP está relacionada a prejuízo da função diastólica e da função sistólica.

2.Determinar frequência e severidade da disfunção sistólica aferida por *strain* miocárdico em pacientes com ICFEP e comparar a função sistólica destes pacientes com pacientes com cardiopatia hipertensiva assintomática e controles saudáveis. Determinar se o prejuízo da função sistólica entre os pacientes com ICFEP é correlacionado a variáveis clínicas, ecocardiográficas e níveis de NT-proBNP.

3.Comparar função atrial esquerda em pacientes com ICFEP e controles saudáveis e determinar as variáveis clínicas e ecocardiográficas que estão associadas a diminuição do *strain* do átrio esquerdo nesses pacientes.

References

[1]McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; ESC Committee for Practice Guidelines.ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803-69.

[2]Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;**128**:e240-327.

[3]Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777-81.

[4]Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation* 2006;**114**:397– 403.

[5]Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;**359**:2456–67.

[6]Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M,McMurray JJ. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;**380**: 1387–95.

[7]Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL,

Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383-92.

[8]Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B; Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013;**309**:781-91.

[9]Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR,Redfield MM. Congestive heart failure in the community: a study of all incidentcases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;**98**:2282–89.

[10]Vasan RS, Larson S, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failurein subjects with normal versus reduced left ventricular ejection fraction: prevalenceand mortality in a population-based cohort. *J Am CollCardiol* 1999;**33**:1948–55.

[11]Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Yanyan G, Liu PP. Outcome ofheart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006**;355**:260–69.

[12]Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *ProgCardiovasc Dis* 2005;**47**:320–32.

[13]Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–59.

[14]Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC; Get With the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012;**126**:65-75.

[15]Bocchi EA, Marcondes-Braga FG, Bacal F, Ferraz AS, Albuquerque D, Rodrigues Dde A, Mesquita ET, Vilas-Boas F, Cruz F, Ramires F, Villacorta H Jr, Souza Neto JD, Rossi Neto JM, Moura LZ, Beck-da-Silva L, Moreira LF, Rohde LE, Montera MW, Simões MV, Moreira Mda C, Clausell N, Bestetti R, Mourilhe-Rocha R, Mangini S, Rassi S, Ayub-Ferreira SM, Martins SM, Bordignon S, Issa VS.[Updating of the Brazilian guideline for chronic heart failure - 2012]. *Arq Bras Cardiol* 2012;**98**:1-33.

[16]Meta-analysis Global Group in Chronic Heart Failure (MAGGIC).The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;**33**:1750-7.

[17]Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA; Candesartan in Heart failure: Assessment of Reduction in

Mortality and morbidity (CHARM) Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007;**116**:1482-87.

[18]Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2011;**13**:18-28.

[19]Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JG, Cody RJ, Chioncel O, Collins SP, Dunnmon P, Filippatos G, Lefkowitz MP, Marti CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopoulou VV, GheorghiadeM. Developing Therapies for Heart Failure With PreservedEjection Fraction: Current State and Future Directions. *JACC Heart Fail* 2014;**2**:97-112.

[20]Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;**350**:1953-9.

[21]Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, Tschöpe C. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation* 2008;**117**:2051-60.

[22]Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *EurHeart J* 2011;**32**:670-9.

[23]Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XH, Deswal A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 2012;**59**:998-1005.

[24]Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263-71.

[25]Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007;**50**:2357-68.

[26]Shah AM and Pfeffer MA.Heart failure: The many faces of heart failure with preserved ejection fraction. *Nature Reviews Cardiology* 2012;**9**,555-56.

[27]Yu C-M, Lin H, Yang H, Kong S-L, ZhangQ, Lee SW-L. Progression of systolic abnormalities in patients with ‘isolated’ diastolic heart failure and diastolic dysfunction. *Circulation* 2002;**105**:1195–1201.

[28]Cioffi G, Senni M, Tarantini L, Faggiano P, Rossi A, Stefenelli C, Russo TE, Alessandro S, Furlanello F, de Simone G. Analysis of circumferential and longitudinal left ventricular systolic function in patients with non-ischemic chronic heart failure and preserved ejection fraction (from the CARRY-IN-HFpEF Study). *Am J Cardiol* 2012;**109**:383–89.

[29]De Sutter J, Van de Veire NR, Muyldermans L, De Backer T, Hoffer E, VaerenbergM,Paelinck B, Decoodt P, Gabriel L, Gillebert TC, Van Camp G; Working Group ofEchocardiography and Cardiac Doppler of the Belgian Society of Cardiology. Prevalenceof mechanical dyssynchrony in patients with heart failure and preserved left ventricular function (a report from the Belgian Multicenter Registry on Dyssynchrony). *Am J Cardiol* 2005;**96**:1543–48.

[30]Yu CM, Zhang Q, YipGW, LeePW,Kum LC, Lam YY, FungJW. Diastolic and systolic asynchrony in patients with diastolic heart failure: a common but ignored condition. *J Am CollCardiol* 2007;**49**:97–105.

[31]Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. *CircCardiovasc Imaging* 2009;**2**:10-15.

[32]Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation* 2006;**113**:296–304.

[33]Carabello BA. Evolution of the study of left ventricular function: everything old is new again. *Circulation* 2002;**105**:2701–03.

[34]Vinch CS, Aurigemma GP, Simon HU, Hill JC, Tighe DA, Meyer TE. Analysis of left ventricular systolic function using midwall mechanics in patients >60 years of age with hypertensive heart disease and heart failure. *Am J Cardiol* 2005;**96**:1299-303.

[35]Petrie MC, Caruana L, Berry C, McMurray JJ."Diastolic heart failure" or heart failure caused by subtle left ventricular systolic dysfunction? *Heart* 2002;**87**:29-31.

[36]Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? *Heart* 2002;**87**:121-25.

[37]Shah AM, Solomon SD. Myocardial deformation imaging: current status and future directions. *Circulation* 2012;**125**:e244-8.

[38]Wang J, Khoury DS, Yue Y, Torre-Amione G, NaguehSF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. *Eur Heart J* 2008;**29**:1283-89.

[39]Yip GW, Zhang Q, Xie JM, Liang YJ, Liu YM, Yan B, Lam YY, Yu CM.Resting global and regional left ventricular contractility in patients with heart failure and normal ejection fraction: insights from speckle-tracking echocardiography. *Heart* 2011;**97**:287-94.

[40]Spragg DD, Kass DA. Pathobiology of left ventricular dyssynchrony and resynchronization. *ProgCardiovasc Dis* 2006;**49**:26-41.

[41]Opdahl A, Remme EW, Helle-Valle T, Lyseggen E, Vartdal T, Pettersen E, Edvardsen T, Smiseth OA. Determinants of left ventricular early-diastolic lengthening velocity: independent contributions from left ventricular relaxation, restoring forces, and lengthening load. *Circulation* 2009;**119**:2578–86.

[42]Bruch C, Stypmann J, Grude M, Gradaus R, Breithardt G, WichterT. Left bundle branch block in chronic heart failure-impact on diastolic function, filling pressures, and B-type natriuretic peptide levels. *J Am SocEchocardiogr* 2006;**19**:95-101.

[43]Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN; Department of Veterans Affairs Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. QRS duration and mortality in patients with congestive heart failure. *Am Heart J* 2002;**143**:1085-91.

[44]Bertoldi EG, Polanczyk CA, Cunha V, Ziegelmann PK, Beck-da-Silva L, Rohde LE. Mortality reduction of cardiac resynchronization and implantable cardioverter-defibrillator therapy in heart failure: an updated meta-analysis. Does recent evidence change the standard of care? *J Card Fail* 2011;**17**:860-66.

[45]Phan TT, Abozguia K, Shivu GN, Ahmed I, Patel K, Leyva F, Frenneaux M. Myocardial contractile inefficiency and dyssynchrony in heart failure with preserved ejection fraction and narrow QRS complex. *J Am SocEchocardiogr* 2010;**23**:201–06.

[46]MorrisDA, Pérez AV, Blaschke F, EichstädtH,Ozcelik C, HaverkampW. Myocardial systolic and diastolic consequences of left ventricular mechanical dyssynchrony in heart failure with normal left ventricular ejection fraction. *Eur Heart J Cardiovasc Imaging* 2012;**13**:556–67.

[47]Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am CollCardiol* 2005;**45**:87-92

[48]Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, Lakatta EG, Najjar SS, KassDA. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. *J Am CollCardiol* 2007;**49**:198-207

[49] Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ, Ostergren J, McKelvie RS; Investigators of the CHARM Echocardiographic Substudy-CHARMES. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. *J Am Coll Cardiol* 2007;**49**:687-94.

[50] Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, Baicu CF, Massie BM, Carson PE; I-PRESERVE Investigators. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation* 2011;**124**:2491-501.

[51] Morris DA, Gailani M, Vaz Pérez A, Blaschke F, Dietz R, Haverkamp W, Ozcelik C. Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. *J Am Soc Echocardiogr* 2011;**24**:651-62.

Artigo 1

Left Ventricular Dyssynchrony in Patients with Heart Failure and Preserved Ejection Fraction

Angela B. S. Santos[1*], Elisabeth Kraigher-Krainer[1*], Natalie Bello[1], Brian Claggett[1], Michael Zile[2], Burkert Pieske[3], Adriaan A. Voors[4], John J.V. McMurray[5], Milton Packer[6], Toni Bransford[7], Marty Lefkowitz[7], Amil Shah[1], Scott D. Solomon[1]

From [1]Brigham and Women's Hospital, Boston, MA, USA; [2]RHJ Department of Veterans Affairs Medical Center and Medical University of South Carolina, Charleston, SC, USA; [3]University of Graz, Graz, Austria; [4]University of Groningen, Groningen, The Netherlands; [5]University of Glasgow, Glasgow, UK; [6]University of Texas Southwestern, Dallas, TX, USA; [7]Novartis Pharmaceuticals, East Hanover, NJ, USA.

Correspondence to Scott D. Solomon, MD, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02445. E-mail ssolomon@rics.bwh.harvard.edu

*Both authors contributed equally to this manuscript.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a common and increasingly prevalent health problem[1] affecting 30 to 55% of all patients with chronic heart failure.[2-5] The pathophysiological mechanisms underlying HFpEF are heterogeneous and complex. While abnormalities of diastolic function including abnormal active relaxation and elevated passive stiffness are most commonly implicated,[6-8] abnormalities of LV systolic function have also been described.[9-11] Additionally mechanisms also appear to contribute to HFpEF, including impaired LV systolic and diastolic functional reserve, pulmonary hypertension and abnormal pulmonary vascular resistance, impaired peripheral oxygen utilization, arterial stiffness and abnormal ventricular-vascular coupling, and chronotropic incompetence.[12]

Cardiac dyssynchrony has been associated with a higher risk of adverse outcomes in heart failure with reduced ejection fraction (HFrEF) and has also been associated with worse prognosis following myocardial infarction.[13] Furthemore mechanical dyssynchrony and its associated inefficiencies in myocardial contraction and relaxation have also been proposed to play a role in HFpEF.[14,15] We used baseline data from the The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Trial, a large well-phenotyped cohort of HFpEF patients, to test the hypothesis that cardiac synchrony is abnormal in HFpEF patients, and that this dyssynchrony is related to impaired diastolic as well as systolic function.

Methods

Study Population

HFpEF Patients

The PARAMOUNT trial (Clinicaltrials.gov NCT00887588) enrolled men and women older than 40 years with left ventricular ejection fraction (LVEF) ≥45%, documented history of heart failure with NYHA class II-IV symptoms, and NT-proBNP levels >400 pg/mL at the baseline visit.[16] Patients were excluded if they had a previous LVEF less than 45% at any time, isolated right heart failure due to pulmonary diseases, dyspnea due to non-cardiac causes such as pulmonary diseases, anemia or severe obesity, primary valvular, coronary or cerebrovascular disease. All of the 301 patients enrolled in the PARAMOUNT trial had a baseline echocardiogram according to a study protocol. A total of 130 patients had apical two- and four-chamber image quality sufficient for speckle tracking analysis, and were appropriate for LV dyssynchrony analysis. Patients with non-DICOM images, missing view(s), poor image quality, left bundle branch block, and/or paced rhythm were excluded (Figure 1).

Controls

A group of 40 healthy controls was retrospectively identified from the medical records of the Brigham and Women's Hospital (BWH). The search strategy targeted patients >55 years who had an echocardiogram, and no ICD-9 code in their record for any of the following conditions: hypertension, ischemic heart disease, cardiac arrhythmia, hypercholesterolemia, chronic obstructive lung disease, diabetes mellitus, cerebrovascular disease, arterial vascular disease, cancer .This group was further selected to have normal LV ejection fraction, no LV regional motion abnormalities, normally sized cardiac chambers, no significant valvular disease and suitable echocardiogram image quality. Controls had a similar age and gender distribution to the HFpEF group. Our final sample was achieved from an initial searching including 2,000 participants. The study protocol was approved by the BWH Institutional Review Board.

Echocardiographic Analyses

Standard echocardiographic and Doppler parameters were analyzed using an offline analysis workstation at a core laboratory (Brigham and Women`s Hospital, Boston MA, USA). All measurements were made in triplicate in accordance with the recommendations of the American Society of Echocardiography[17,18] and included LV diameter and volumes, LV wall thickness, LV mass, LVEF, LA volume, mitral inflow propagation and lateral mitral annular relaxation velocities.

Dyssynchrony and contractile function indices were measured using B-mode speckle-tracking software (TomTec Imaging Systems, Unterschleissheim, Germany) that circumvents angle dependency and identifies cardiac motion by tracking multiple reference points over time. The endocardial borders were traced at the end-diastolic frame of 2D images acquired from the apical two- and four-chamber views. End-diastole was defined by the QRS complex, or as the frame after mitral valve closure. Speckles were tracked frame by frame throughout the LV myocardium over the course of one cardiac cycle; basal, mid, and apical regions of interest were then created. Thereafter each image was carefully inspected and the segments that failed to track were manually adjusted. If more than 1 segment could not be tracked, if there was a lack of a full cardiac cycle or significant foreshortening of the left ventricle, the measurements were considered unreliable and the patient was excluded from the analysis. Mechanical dyssynchrony of the LV was measured as the standard deviation of regional time-to-peak longitudinal strain (in milliseconds) measured during systole, across the 12 anatomic wall segments of the apical four- and two-chambers views (Figure 2).[14] Global longitudinal strain was calculated as the average longitudinal strain across the apical two- and four-chamber views. For patients in sinus rhythm, analyses were performed on a single cardiac cycle, while for patients in atrial fibrillation strain values were averaged over 3 cardiac cycles. Intra-observer variability was assessed in 30

randomly selected PARAMOUNT studies: coefficient of variation: 6.8%; intra-class correlation coefficient was 0.95 (95% CI 0.91-0.98) for global longitudinal strain.

Statistical analysis

All normally distributed data were displayed as mean and standard deviation, and non-normally distributed data were displayed as median and interquartile range. Categorical data were shown as a total number and proportion. NT-proBNP was log-transformed before analysis. Categorical variables were compared using X^2 tests and continuous variables were compared using a two sided *t*-test with unequal variance.

We categorized the HFpEF patients in quartiles according to severity of dyssynchrony, and applied trend tests across ordered groups to illustrate the association between dyssynchrony and demographic characteristics, NTproBNP levels, QRS interval and echocardiographic measures of cardiac structure and function. Correlations of categorical and continuous variables were tested by Pearson's coefficient. Multivariate linear regression analysis was performed to adjust for significant clinical variables. All tests were two-sided and p-values of <0.05 were considered statistically significant. Stata/SE version 12.1 (StataCorp, College Station, TX) was used for all analysis.

Results

Patient characteristics

Patients with HFpEF were generally elderly, obese, and mostly women (62%) (Table 1). Most of these patients were in NYHA functional class II (77%), and had elevated NTproBNP levels (median 867 pg/mL, IQR 482 to 1459 pg/mL). Although the majority of patients were hypertensive (92%), their blood pressure was well controlled. Atrial fibrillation was present in 24 (18%) patients at the time of echocardiography. The mean QRS duration was 96.1±21.6ms and

17 (13%) patients had QRS duration greater than or equal to 120ms. Patients included in this analysis had slightly higher ejection fraction (59.6 ± 7.2% vs. 56.6 ± 7.9%, p<0.001), and had higher systolic blood pressure (139 ± 15mmHg vs. 133 ± 15mmHg, p=0.002) than patients not included, but were similar with respect to other baseline characteristics.

Compared with controls, patients with HFpEF had lower ejection fraction, though still within the normal range, and global longitudinal strain was lower. HFpEF patients had also higher left ventricular (LV) and left atrial (LA) volumes, lower mitral annular relaxation velocity (E') and higher E/E' ratio compared to controls. The LV mass was not different between groups. The relative wall thickness was higher in controls than HFpEF patients driven by higher LV end diastolic diameter in the HFpEF group (Table 1). The elevated NT-proBNP, as inclusion criteria in the PARAMOUNT trial, can favor patients with larger left ventricles. Indeed, in our study, LV end diastolic diameter was significantly associated with NT-proBNP levels (p=0.03).

Cardiac Dyssynchrony

LV dyssynchrony was significantly worse in HFpEF patients compared with controls (Figure 3). The difference between these groups persisted even when the analysis was restricted to HFpEF patients in sinus rhythm (n=106; 56.4 ± 33.5ms in controls vs. 97.6 ± 51.8ms in HFpEF, p<0.001) or to 40 HFpEF patients (age and gender matched 1:1 with controls). Also, the differences remain in a subset of HFpEF patients with EF ≥55% and QRS≤100ms (n = 63; 56.4 ± 33.5ms in controls vs. 88.5 ± 55.8ms in HFpEF, p<0.001), and remained significant after adjustment for age, gender, systolic blood pressure, LV mass index and ejection fraction (p=0.013).

Amongst HFpEF patients, those with more dyssynchrony had wider QRS intervals, higher LV mass indices, and progressively decreased mitral annular relaxation velocity (E')

compared to HFpEF patients in the lowest quartile of dyssynchrony (Table 2). LV ejection fraction, global longitudinal strain, left atrial volume index, E/E', and NT-proBNP did not differ based on the degree of dyssynchrony. In a sensitivity analysis, the relationship between dyssynchrony and E' persisted even in patients with ejection fraction ≥55%, and after adjustment for age, gender, systolic blood pressure, LV mass index and LV ejection fraction (Figure 4).

Discussion

We observed that HFpEF patients had greater LV dyssynchrony compared with healthy controls and that dyssynchrony was present even in patients with LVEF ≥55% and narrow QRS. In HFpEF patients, worse LV dyssynchrony was associated with a wider QRS interval, lower mitral annular relaxation velocity, and higher LV mass. These findings suggest that dyssynchrony may play a pathophysiologic role in HFpEF.

In addition to the acknowledged association between HFrEF and dyssynchrony,[19-21] LV dyssynchrony has also been described in HFpEF. Studies using conventional Doppler echocardiography parameters and Tissue Doppler (TDI) first demonstrated that mechanical dyssynchrony is common in patients with HFpEF, regardless of QRS duration.[14,22,23] Recently, speckle tracking has emerged as a more robust technique to quantify dyssynchrony because unlike Doppler it is angle independent.[24] Phan *et al* compared 33 HFpEF patients with a narrow QRS (<120ms) to healthy controls, and showed greater dyssynchrony in the former.[14] More recently, speckle tracking was used to demonstrate that 85 HFpEF patients had greater dyssynchrony than patients with asymptomatic LV diastolic dysfunction.[15] Our study utilized speckle tracking, all echocardiography measurements were performed using a core laboratory[25] and included the largest sample of HFpEF patients to date. We further showed that greater

dyssynchrony was present even in HFpEF patients with ejection fraction >55%[17] and a narrower QRS (<100ms) than previously reported.

We found that greater LV dyssynchrony was most robustly associated with lower early diastolic relaxation assessed by E'. The association remained strong even in a subset of patients with robustly preserved ejection fraction. Temporal heterogeneity in systolic function may play an important pathophysiological role in HFpEF by interrupting the normally tightly coordinated relationship between systolic shortening and subsequent diastolic lengthening.[26] As dyssynchrony increases, it can result in decreasing of systolic shortening which has been shown to increase diastolic filling pressure.[27-29] We did not find a relationship between the degree of LV dyssynchrony and LV filling pressure (E/E'), which might result from our use of a narrower range of patients, selected for elevated NTproBNP levels. The relationship seen between mechanical dyssynchrony and increased LV mass suggests that LV hypertrophy and/or interstitial fibrosis may be associated with dyssynchrony in HFpEF. Although there is a well-described association between LV dyssynchrony and systolic dysfunction in HFrEF[24] we could not demonstrate one in our HFpEF cohort.

The degree of dyssynchrony observed in these HFpEF patients was considerably less than typically observed in HFrEF patients being considered for cardiac resynchronization therapy (CRT)[30,31] (126±7.8ms in HFrEF patients from MADIT-CRT[32] vs 90.6±4.5ms in our HFpEF cohort) and less than what has been previously observed in post-MI patients.[33] To date, little evidence exists to demonstrate CRT is beneficial in patients with preserved ejection fraction, although one study showed a clinical and structural benefit from CRT in patients with mean LVEF 43±7%.[34] We therefore cannot rule out the possibility that dyssynchrony plays a

pathophysiologic role in HFpEF, albeit in conjunction with other abnormalities of cardiac function.

Some limitations of this analysis should be noted. Only half of the patients enrolled in the PARAMOUNT trial had echocardiograms that were eligible for dyssynchrony evaluation by combined two-chamber and four-chamber 2D speckle tracking analysis. While there were some differences between the included cohort and those who could not be included - ejection fraction was even higher in the patients analyzed. There is no gold standard to assess cardiac dyssynchrony, but speckle tracking appears to be more accurate than Doppler-based techniques.[24] Because PARAMOUNT was a clinical trial, the generalizability of these findings to HFpEF patients in the community may be limited due to the inclusion/exclusion criteria of the PARAMOUNT trial.

In summary, we found greater LV mechanical dyssynchrony in HFpEF patients compared with healthy controls, even among those with robustly preserved LVEF and no significant electrical dyssynchrony. In HFpEF, greater mechanical dyssynchrony appears to be associated with wider QRS, greater myocardial hypertrophy, and especially impaired diastolic, but not systolic function, suggesting that mechanical dyssynchrony may play a pathophysiologic role in HFpEF. The prognostic relevance of mechanical dyssynchrony and the potential role of CRT in HFpEF remain to be determined.

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Table 1: Baseline characteristics of the study population

	Controls (n=40)	**HFpEF (n=130)**	**p value**
Age (years)	69 ± 7	71 ± 9	0.11
Women, n (%)	31 (78)	80 (62)	0.06
NYHA II, n (%)	--	100 (77)	
NYHA III, n (%)	--	29 (22)	
Previous Hospitalization for HF, n (%)	0 (0%)	64 (49)	
History of Atrial Fibrillation, n (%)	0 (0%)	57 (44)	
History of Hypertension, n (%)	0 (0%)	119 (92)	
History of Diabetes, n (%)	0 (0%)	43 (33)	
History of Myocardial Infarction, n (%)	0 (0%)	26 (20)	
Heart Rate (beats per min)	69 ± 12	69 ± 14	0.96
Systolic Blood Pressure (mm Hg)	129 ± 15	139 ± 15	0.002
Diastolic Blood Pressure (mm Hg)	74 ± 10	78 ± 10	0.04
Body Mass Index (kg/m^2)	25.9 ± 4.0	30.2 ± 5.9	<0.001
NT-proBNP (pg/mL)	--	867 [482,1459]	
Echocardiographic measures			
LV Ejection Fraction (%)	65.2 ± 4.8	59.6 ± 7.3	<0.001
Global Longitudinal Strain (%)	-20.0 ± 2.1	-15.1 ± 3.1	<0.001
LV End-Diastolic Volume (mL)	82.9 ± 18.3	111.9 ± 27.9	<0.001
LV End-Systolic Volume (mL)	28.8 ± 7.5	45.7 ± 16.5	<0.001

LV End-Diastolic Volume/BSA (mL/m^2)	47.1 ± 9.4	60.3 ± 13.4	<0.001
LV End-Systolic Volume/BSA (mL/m^2)	16.6 ± 4.4	24.6 ± 8.4	<0.001
Relative Wall Thickness (%)	0.41 ± 0.07	0.38 ± 0.08	0.008
LV Mass/BSA (g/m^2)	80.3 ± 17.5	77.4 ± 21.6	0.40
LV Mass/Height$^{2.7}$ (g/$m^{2.7}$)	37.2 ± 8.3	38.4 ± 11.2	0.49
E' (cm/s)	8.8 ± 2.1	7.3 ± 2.7	<0.001
E/E'	8.3 ± 3.2	13.2 ± 6.5	<0.001
E/A	0.93 ± 0.22	1.21 ± 0.71	0.001
Left Atrial Volume/BSA (mL/m^2)	21.7 ± 5.6	35.5 ± 12.0	<0.001

Data are presented as n (%), mean ± SD, median [IQR].

p values was calculated by t-test or X^2

NYHA= New York Heart Association. BSA= body surface area. E'= lateral mitral relaxation velocity. E/E'=mitral inflow to mitral relaxation velocity ratio. E/A=early to late mitral inflow velocity ratio.

Table 2 Characteristics of HFpEF patients by quartiles of left ventricular longitudinal dyssynchrony

	Quartiles of LV longitudinal dyssynchrony				
	Better			**Worse**	
	39.6 ± 7.2ms (n=33)	64.0 ± 6.3ms (n=32)	93.5 ± 9.9ms (n=33)	166.6 ± 33.6ms (n=32)	p value for trend
Age (years)	71 ± 7	70 ± 9	70 ± 9	72 ± 10	0.49
Women, n (%)	22 (67)	21 (66)	18 (55)	19 (59)	0.39
SBP (mm Hg)	136 ± 14	135 ± 17	141 ± 16	141 ± 14	0.10
NYHA III, n (%)	5 (15%)	8 (25%)	8 (24%)	8 (25%)	0.37
QRS (ms)	91 ± 13	97 ± 22	93 ± 16	104 ± 30	0.04
NT-proBNP(pg/mL)	911 [635,1314]	834 [548,1397]	863 [407,1725]	867 [439,1557]	0.75
LVEF (%)	59.9 ± 7.0	59.4 ± 6.1	58.8 ± 7.5	60.4 ± 8.5	0.94
GL strain (%)	-15.7 ± 3.2	-15.3 ± 3.4	-14.9 ± 2.6	-14.6 ± 3.2	0.12
LV end-diastolic volume (mL)	108.4 ± 29.7	108.6 ± 32.9	116.5 ± 24.5	114.1 ± 24.1	0.25
LV end-systolic volume (mL)	44.0 ± 18.0	44.3 ± 16.5	48.4 ± 14.6	46.1 ± 17.3	0.43
LV mass/BSA (g/m^2)	72.2 ± 25.4	75.3 ± 20.3	79.5 ± 18.4	82.6 ± 21.1	0.04
RWT	0.36 ± 0.06	0.39 ± 0.08	0.37 ± 0.07	0.40 ± 0.11	0.14
E' (cm/s)	8.1 ± 2.8	8.0 ± 2.9	6.9 ± 2.1	6.1 ± 2.8	0.001
E/E'	12.8 ± 5.5	13.0 ± 6.1	12.5 ± 5.5	14.6 ± 8.7	0.36
LAV/BSA (mL/m^2)	40.1 ± 14.2	33.5 ± 8.4	33.8 ± 10.8	34.5 ± 13.0	0.07

Data are presented as n (%), mean ± SD, median [IQR].

NYHA= New York Heart Association. SBP=systolic blood pressure LVEF= left ventricular ejection fraction. GL strain=global longitudinal strain. RWT= relative wall thickness. E'= lateral mitral relaxation velocity. E/E'=mitral inflow to mitral relaxation velocity ratio. LAV= left atrial volume.

References

[1] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2006;**355**:251–259.

[2] Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MMl. Congestive Heart Failure in the Community: A Study of All Incident Cases in Olmsted County, Minnesota, in 1991. *Circulation* 1998;**98**:2282–2289.

[3] Vasan RS, Larson S, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;**33**:1948–1955.

[4] Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Yanyan G, Liu PP. Outcome of Heart Failure with Preserved Ejection Fraction in a Population-Based Study. *N Engl J Med* 2006;**355**:260–269.

[5] Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;**33**:1750–1757.

[6] Zile MR, Baicu CF, Gaasch WH. Diastolic Heart Failure — Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle. *New Engl J Med* 2004;**350**:1953–1959.

[7] Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, Baicu CF, Masiie BM, Carson PE. Prevalence and Significance of Alterations in Cardiac Structure and Function in Patients With Heart Failure and a Preserved Ejection Fraction. *Circulation* 2011;**124**:2491–2501.

[8] Wachter R, Schmidt-Schweda S, Westermann D, Post H, Edelmann F, Kasner M, Lüers C, Steendijk P, Hasenfuss G, Tschöpe C, Pieske B. Blunted frequency-dependent upregulation of

cardiac output is related to impaired relaxation in diastolic heart failure. *Eur Heart J* 2009;**30**:3027-3036.

[9] Yu C-M, Lin H, Yang H, Kong S-L, Zhang Q, Lee SW-L. Progression of Systolic Abnormalities in Patients With "Isolated" Diastolic Heart Failure and Diastolic Dysfunction. *Circulation* 2002;**105**:1195–1201.

[10] Kang SJ, Lim HS, Choi BJ, Choi SY, Hwang GS, Yoon MH, Tahk SJ, Shin JH. Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. *J Am Soc Echocardiogr* 2008;**21**:907–911.

[11] Cioffi G, Senni M, Tarantini L, Faggiano P, Rossi A, Stefenelli C, Russo TE, Alessandro S, Furlanello F, de Simone G. Analysis of Circumferential and Longitudinal Left Ventricular Systolic Function in Patients With Non-Ischemic Chronic Heart Failure and Preserved Ejection Fraction (from the CARRY-IN-HFpEF Study). *Am J Cardiol* 2012;**109**:383–389.

[12] Shah A M and Pfeffer MA. The many faces of heart failure with preserved ejection fraction**.** *Nat. Rev. Cardiol* 2012;**9**, 555–556.

[13] Shin S-H, Hung C-L, Uno H, Hassanein AH, Verma A, Bourgoun M, Kober L, Ghali JK, Velazquez EJ, Callif RM, Pfeffer MA, Solomon SD. Mechanical dyssynchrony after myocardial infarction in patients with left ventricular dysfunction, heart failure, or both. *Circulation* 2010;**121**:1096–103.

[14] Phan TT, Abozguia K, Shivu GN, Ahmed I, Patel K, Leyva F, Frenneaux M. Myocardial Contractile Inefficiency and Dyssynchrony in Heart Failure With Preserved Ejection Fraction and Narrow QRS Complex. *J Am Soc Echocardiogr* 2010;**23**:201–6.

[15] Morris DA, Pérez AV, Blaschke F, Eichstädt H, Özcelik C, Haverkamp W. Myocardial systolic and diastolic consequences of left ventricular mechanical dyssynchrony in heart failure with normal left ventricular ejection fraction. *Eur Heart J Cardiovasc Imaging* 2012;**13**:556–567.

[16] Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;**380**:1387–95.

[17] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;**18**:1440-63.

[18] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107–133.

[19] Yu C-M, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart* 2003;**89**:54–60.

[20] Aydin M, Demircan N, Cam F, Dogan SM, Yildirim N, Karabag T, Aktop Z, Sayin MR. Assessment of left ventricular systolic and diastolic dyssynchrony with tissue Doppler echocardiography in patients with heart failure and narrow QRS complex. *Minerva Cardioangiol* 2012;**60**:581–592.

[21] Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE; ESC Committee for Practice Guidelines (CPG), Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bänsch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA).*Eur Heart J* 2013;**34**:2281-329.

[22] De Sutter J, Van de Veire NR, Muyldermans L, De Backer T, Hoffer E, Vaerenberg M, Paelinck B, Decoodt P, Gabriel L, Gillebert TC, Van Camp G; Working Group of Echocardiography and Cardiac Doppler of the Belgian Society of Cardiology. Prevalence of Mechanical Dyssynchrony in Patients With Heart Failure and Preserved Left Ventricular

Function (a Report from the Belgian Multicenter Registry on Dyssynchrony). *Am J Cardiol* 2005;**96**:1543–8.

[23] Yu CM, Zhang Q, Yip GW, Lee PW, Kum LC, Lam YY, Fung JW. Diastolic and Systolic Asynchrony in Patients With Diastolic Heart Failure: A Common But Ignored Condition. *J Am Coll Cardiol* 2007;**49**:97–105.

[24] Pouleur AC, Knappe D, Shah AM, Uno H, Bourgoun M, Foster E, McNitt S, Hall WJ, Zareba W, Goldenberg I, Moss AJ, Pfeffer MA, Solomon SD; MADIT-CRT Investigators. Relationship between improvement in left ventricular dyssynchrony and contractile function and clinical outcome with cardiac resynchronization therapy: the MADIT-CRT trial. *Eur Heart J* 2011;**32**:1720–1729.

[25] Douglas PS, DeCara JM, Devereux RB, Duckworth S, Gardin JM, Jaber WA, Morehead AJ, Oh JK, Picard MH, Solomon SD, Wei K, Weissman NJ; American Society of Echocardiography Standards; American College of Cardiology Foundation. Echocardiographic imaging in clinical trials: American Society of Echocardiography Standards for echocardiography core laboratories: endorsed by the American College of Cardiology Foundation. *J Am Soc Echocardiogr* 2009;**22**:755-765.

[26] Opdahl A, Remme EW, Helle-Valle T, Lyseggen E, Vartdal T, Pettersen E, Edvardsen T, Smiseth OA. Determinants of left ventricular early-diastolic lengthening velocity: independent contributions from left ventricular relaxation, restoring forces, and lengthening load. *Circulation* 2009;**119**:2578-2586.

[27] Lew WY, Rasmussen CM. Influence of nonuniformity on rate of left ventricular pressure fall in the dog. *Am J Physiol* 1989;**256**:222-232.

[28] Kuznetsova T, Bogaert P, Kloch-Badelek M, Thijs D, Thijs L, Staessen JA. Association of left ventricular diastolic function with systolic dyssynchrony: a population study. *Eur Heart J Cardiovasc Imaging* 2013;**14**:471-479.

[29] Ciampi Q, Petruzziello B, Della Porta M, Caputo S, Manganiello V, Astarita C, Villari B. Effect of intraventricular dyssynchrony on diastolic function and exercise tolerance in patients with heart failure *Eur J Echocardiogr* 2009;**10**:907-913.

[30] Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329 –1338.

[31] Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators.Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.

[32] Knappe D, Pouleur AC, Shah AM, Bourgoun M, Brown MW, Foster E, Pfeffer MA, Moss AJ, Solomon SD; MADIT-CRT Investigators. Acute effects of withdrawal of cardiac resynchronization therapy on left and right ventricular function, dyssynchrony, and contractile function in patients with New York Heart Association functional class I/II heart failure: MADIT-CRT. *J Card Fail* 2013;**19**:149-155.

[33] Mollema SA, Liem SS, Suffoletto MS, Bleeker GB, van der Hoeven BL, van de Veire NR, Boersma E, Holman ER, van der Wall EE, Schalij MJ, Gorcsan J 3rd, Bax JJ. Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling. *J Am Coll Cardiol* 2007;**50**:1532–1540.

[34] Chung ES, Katra RP, Ghio S, Bax J, Gerritse B, Hilpisch K, Peterson BJ, Feldman DS, Abraham WT. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Failure* 2010;**12**:581-587.

Legends

Figure 1 Feasibility of dyssynchrony evaluation by speckle-tracking analysis.

Figure 2 Two-dimensional speckle tracking imaging in the apical four-chamber view in a healthy control patient (left panel) and a patient with HFpEF (right panel). Curves represent longitudinal strain curves, which were used to measure left ventricular dyssynchrony and contractile function.

Figure 3 Left ventricular dyssynchrony in HFpEF and healthy controls. Data are presented as mean + SE.

Figure 4 Diastolic function by quartiles of severity of LV dyssynchrony in HFpEF (EF≥55%). Data are presented as mean ± SE. P value adjusted by age, gender, systolic blood pressure, LV mass, LV ejection fraction.

Figure 1

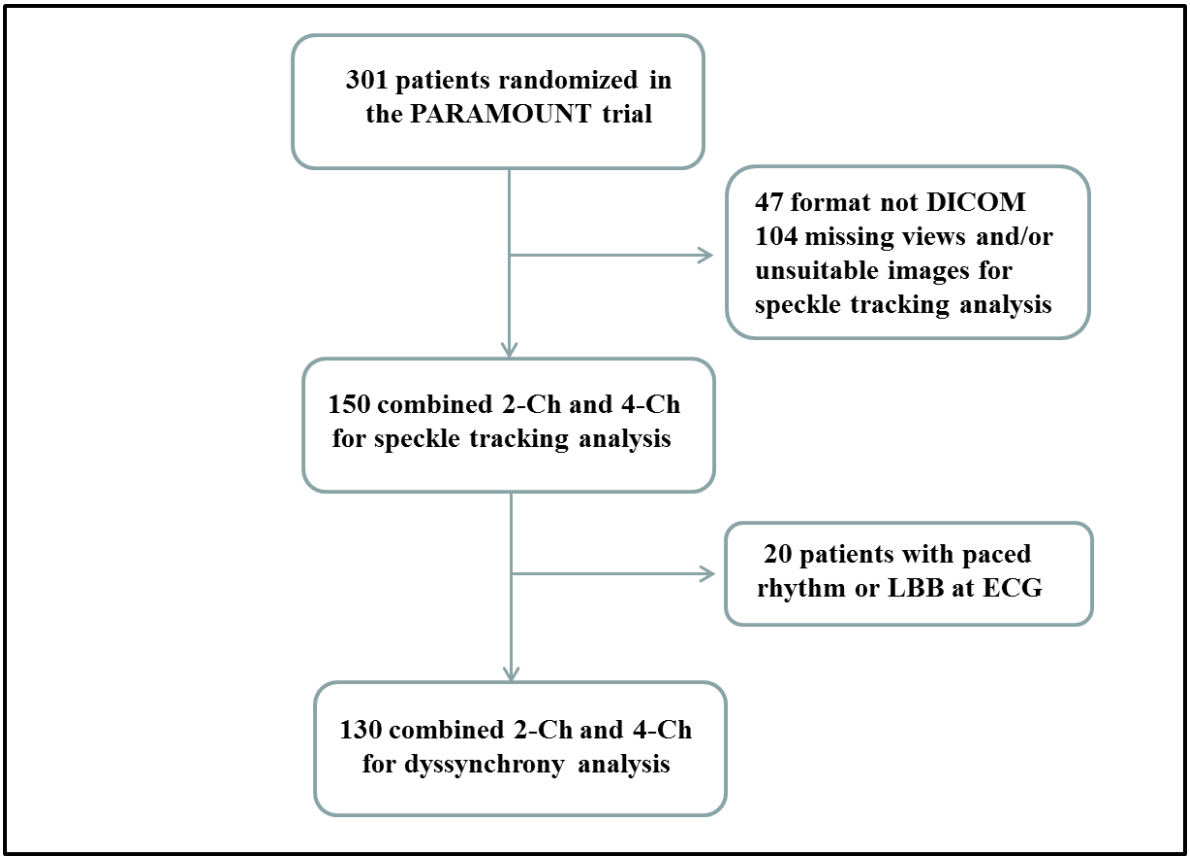

301 patients randomized in the PARAMOUNT trial
47 format not DICOM
104 missing views and/or unsuitable images for speckle tracking analysis
150 combined 2-Ch and 4-Ch for speckle tracking analysis
20 patients with paced rhythm or LBB at ECG
130 combined 2-Ch and 4-Ch for dyssynchrony analysis

Figure 2

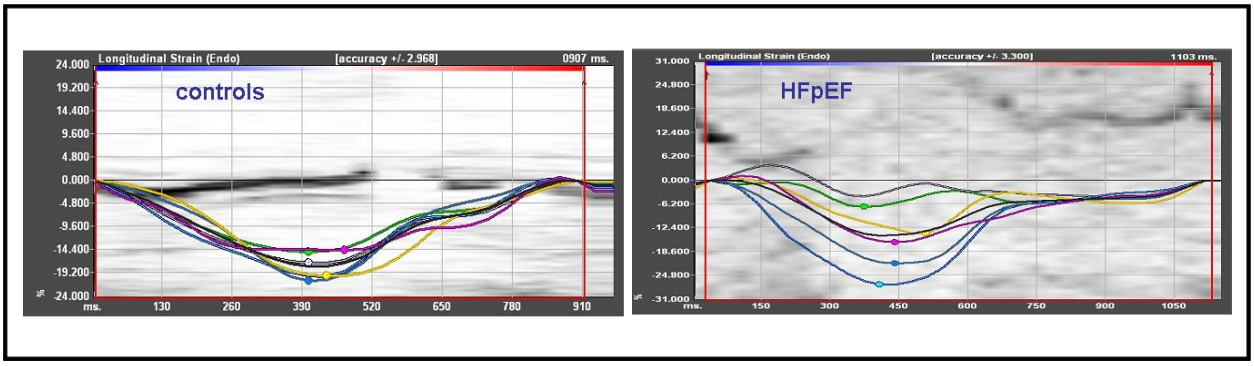

Longitudinal Strain (Endo)
[accuracy +/- 2.968]
0907 ms.
controls
24.000
19.200
14.400
9.600
4.800
0.000
-4.800
-9.600
-14.400
-19.200
-24.000
%
ms.
130
260
390
520
650
780
910
Longitudinal Strain (Endo)
[accuracy +/- 3.300]
1103 ms.
HFpEF
31.000
24.800
18.600
12.400
6.200
0.000
-6.200
-12.400
-18.600
-24.800
-31.000
%
ms.
150
300
450
600
750
900
1050

Figure 3

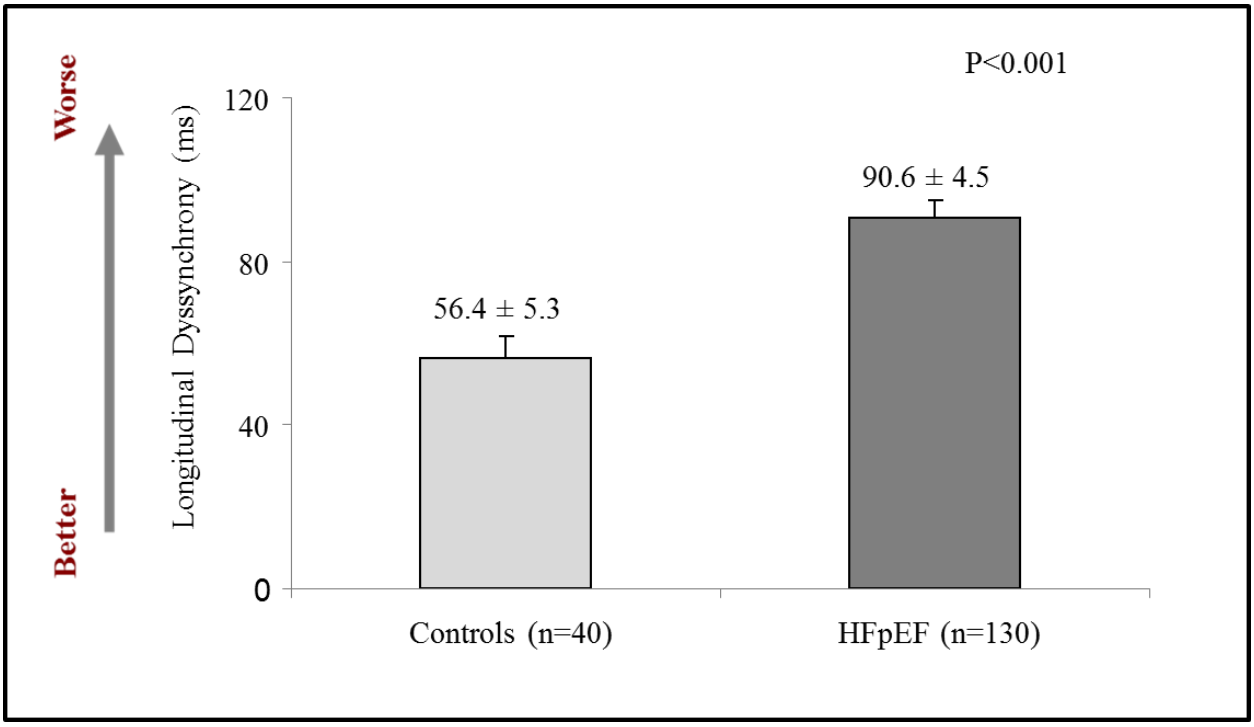
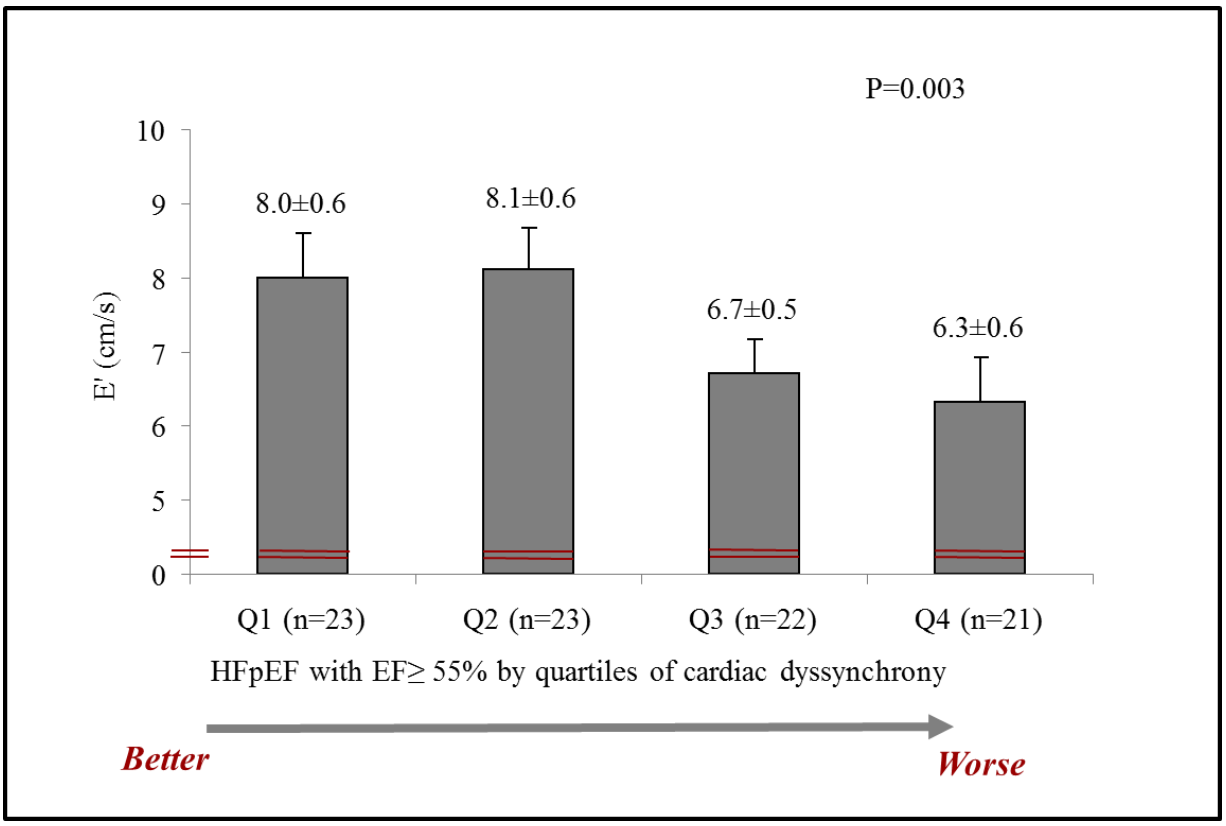

Worse
Better
Longitudinal Dyssynchrony (ms)
120
80
40
0
P<0.001
56.4 ± 5.3
90.6 ± 4.5
Controls (n=40)
HFpEF (n=130)

Figure 4


P=0.003
10
9
8
7
6
5
0
E' (cm/s)
8.0±0.6
8.1±0.6
6.7±0.5
6.3±0.6
Q1 (n=23)
Q2 (n=23)
Q3 (n=22)
Q4 (n=21)
HFpEF with EF≥ 55% by quartiles of cardiac dyssynchrony
Better
Worse

Artigo 2

Impaired Systolic Function by Strain Imaging in Heart Failure With Preserved Ejection Fraction

Elisabeth Kraigher-Krainer, MD,[1]* Amil M. Shah, MD, MPH, [1]* Deepak K. Gupta, MD, [1] Angela Santos, MD, [1] Brian Claggett, PHD, [1] Burkert Pieske, MD,[2] Michael R. Zile, MD,[3]

Adriaan A. Voors, MD,[4] Marty P. Lefkowitz, MD,[5] Milton Packer, MD, [6] John J. V. McMurray, MD, [7]Scott D. Solomon, MD, [1] for the PARAMOUNT Investigators

From: Boston, Massachusetts[1]; Graz, Austria[2]; Charleston, South Carolina[3]; Groningen, the Netherlands[4]; East Hanover, New Jersey[5]; Dallas, Texas[6]; and Glasgow, United Kingdom[7]

Correspondence to Scott D. Solomon, MD, Cardiovascular Division, Brigham and Women's Hospital; 75 Francis St, Boston, MA 02445; Tel: 857-307-1960/ Fax: 857-307-1944; E-mail ssolomon@rics.bwh.harvard.edu

*Both authors contributed equally to this article.

Abstract

Objectives: This study sought to determine the frequency and magnitude of impaired systolic deformation in heart failure with preserved ejection fraction (HFpEF).

Background: Although diastolic dysfunction is widely considered a key pathophysiologic mediator of HFpEF, the prevalence of concomitant systolic dysfunction has not been clearly defined.

Methods: We assessed myocardial systolic and diastolic function in 219 HFpEF patients from a contemporary HFpEF clinical trial. Myocardial deformation was assessed using a vendor-independent 2-dimensional speckle-tracking software. The frequency and severity of impaired deformation was assessed in HFpEF, and compared to 50 normal controls free of cardiovascular disease and to 44 age- and sex-matched hypertensive patients with diastolic dysfunction (hypertensive heart disease) but no HF. Among HFpEF patients, clinical, echocardiographic, and biomarker correlates of left ventricular strain were determined.

Results: The HFpEF patients had preserved left ventricular ejection fraction and evidence of diastolic dysfunction. Compared to both normal controls and hypertensive heart disease patients, the HFpEF patients demonstrated significantly lower longitudinal strain (LS) (-20.0 ± 2.1 and -17.07 ± 2.04 vs. -14.6 ± 3.3, respectively, $p < 0.0001$ for both) and circumferential strain (CS) (-27.1 ± 3.1 and -30.1 ± 3.5 vs. -22.9 ± 5.9, respectively; $p < 0.0001$ for both). In HFpEF, both LS and CS were related to LVEF (LS, $R = -0.46$; $p < 0.0001$; CS, $R = -0.51$; $p < 0.0001$) but not to standard echocardiographic measures of diastolic function (E' or E/E'). Lower LS was modestly associated with higher NT-proBNP, even after adjustment for 10 baseline covariates

including LVEF, measures of diastolic function, and LV filling pressure (multivariable adjusted p = 0.001).

Conclusions: Strain imaging detects impaired systolic function despite preserved global LVEF in HFpEF that may contribute to the pathophysiology of the HFpEF syndrome. (LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction; NCT00887588)

Heart failure with preserved ejection fraction (HFpEF) is a prevalent and growing public health problem associated with significant morbidity and an increased risk of in-hospital, short-term, and long-term mortality (1,2). Impairment in LV diastolic function has been proposed as a key pathophysiologic mediator (3–5). However, the role of concomitant systolic dysfunction despite preserved left ventricular ejection fraction (LVEF) has not been well characterized, but may help inform future treatment strategies by defining subphenotypes in this heterogeneous population. Indeed, prior studies suggest that LV longitudinal function assessed by tissue Doppler imaging may be impaired in HFpEF (6–11). However, tissue Doppler-based assessment of LV longitudinal function is angle dependent and typically assesses only mitral annular motion.

More recently, B-mode speckle tracking has allowed for quantitative assessment of LV deformation, and abnormalities of strain and strain rate have been described in HFpEF in several small single center studies (12–15). We employed myocardial deformation imaging to determine the frequency, severity, and correlates of impaired systolic function among patients with HFpEF enrolled in a contemporary multicenter clinical trial. Specifically, we hypothesized that despite preserved LVEF, abnormal strain would be prevalent in HFpEF, differentiate HFpEF from asymptomatic hypertensive heart disease (HHD), and would relate to levels of Nterminal pro-brain

natriuretic peptide (NT-proBNP), a soluble biomarker of myocardial wall stress with prognostic relevance in HFpEF, independent of measures of diastolic function.

Methods

Patient population. The PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Trial) study enrolled patients with signs and symptoms of heart failure (HF), New York Heart Association class II to IV symptoms, LVEF _45%, and NT-proBNP level >400 pg/ml. Patients were randomly allocated to receive either the angiotensinreceptor neprilysin inhibitor (ARNI) LCZ696 or valsartan

over a period of 12 weeks. The study protocol was approved by all individual site institutional review boards and ethics committees, and all recruited patients gave written informed consent. Details of the inclusion and exclusion criteria, study design and primary findings have been previously reported (16). Screening NT-proBNP was established by a tabletop device at point of care, local laboratory, or central laboratory. No NT-proBNP data were available for the HHD group or control population.

Control group. We screened the Brigham and Women's Hospital's echocardiography database to retrospectively identify normal control subjects. Echocardiographic examinations were clinically indicated for 1 of the following reasons: murmur, evaluation of LV function, syncope, or atypical chest pain. Normal echocardiograms were defined asnormal LV size and geometry, normal LVEF (>55%), normal left atrial volume index (LAVi) (<29 ml/m2) (17),no stenotic valvular lesion, and no abnormal valvular regurgitation. Electronic medical records were reviewed for prevalent cardiovascular disease (stroke, coronary artery disease, myocardial infarction, revascularization, heart failure, arrhythmia, peripheral artery disease), cardiovascular

risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking, renal dysfunction), systemic disease (such as cancer, infections, autoimmune disorders), or any pharmacotherapy. Subjects were excluded if any of these were identified. In all, 2,100 echocardiographic examinations and medical records performed between 2010 and 2012 were screened to identify 50 controls of similar age and sex distribution as our HFpEF cohort. Hypertensive group with diastolic dysfunction but no HF. We identified 44 patients with hypertension and diastolic dysfunction matched to the HFpEF population for age and sex. They were selected from patients enrolled in the EXCEED (Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic dysfunction) trial. Details of the inclusion and exclusion criteria, study design, and primary findings have been previously published (18,19). Briefly, the EXCEED trial was a multicenter, open-label study of patients ≥45 years of age with a history of uncontrolled systolic hypertension, preserved LVEF (≥50%), and echocardiographic evidence of diastolic dysfunction. Patients with HF symptoms, secondary hypertension, diabetes, atrial fibrillation, a vascular event within the prior 6 months, serum creatinine >2.0 mg/dl, or nephrotic syndrome were excluded. All participants underwent echocardiography at enrollment, which was analyzed centrally by the same core laboratory as the PARAMOUNT study (Brigham and Women's Hospital, Boston, Massachusetts). Echocardiographic analyses. All sonographers at participating sites underwent central training in the details of the echocardiographic views and techniques at study investigator meetings. Echocardiograms were performed at study enrollment and were sent on digital storage media to the echocardiography core laboratory at Brigham and Women's Hospital. Conventional echocardiographic analysis including 2-dimensional, Doppler, and tissue Doppler were performed by technicians blinded to clinical information and treatment assignment using an offline analysis work station, as

previously described in detail (20). Ventricular volumes were calculated by the modified Simpson's method using the apical 4- and 2-chamber views, and LVEF was derived from volumes in the standard manner (17). The LV mass was calculated from LV linear dimensions and indexed to body surface area as recommended by American Society of Echocardiography guidelines. Left ventricular hypertrophy was defined as LV mass indexed to body surface area (LVMi) >115 g/m2 in men or >95 g/m2 in women. The relative wall thickness (RWT) was calculated from LV end-diastolic dimension and posterior wall thickness. The left atrial (LA) volume was measured by the biplanethe end-systolic frame preceding mitral valve opening, and was indexed to body surface area to derive LAVi. Early transmitral velocity (E wave) was measured by pulsed wave Doppler from the apical 4-chamber view with the sample volume positioned at the tip of the mitral leaflets. Tissue Doppler derived peak longitudinal systolic shortening velocity (S´) was obtained in the apical 4-chamber view at the lateral and septal mitral annulus and averaged. Peak left ventricular relaxation velocity (E') was obtained from the lateral and septal mitral annulus and averaged. The E/E' ratio was calculated as E wave divided by E' velocities. Diastolic dysfunction grade was derived from mitral inflow E/A ratio, tissue Doppler septal E', and deceleration time (21). All measurements were performed in triplicate. Digitally acquired baseline echocardiography images in Digital Imaging and Communications in Medicine (DICOM) format with acceptable image quality were uploaded to the TomTec system (Munich, Germany) for further deformational analyses (Cardiac Performance Analysis software, TomTec). These methods have been validated against magnetic resonance imaging and sonomicrometry (22,23), and we have previously reported excellent reproducibility (24–26). A total of 219 patients of the total PARAMOUNT patient population of 301 participants (73% of total enrolled) had adequate echocardiographic

image quality for deformational analysis by B-mode speckle tracking. Unacceptable image quality was defined as lack of a full cardiac cycle, >1 segment dropout, digital format other than DICOM, missing view, or significant foreshortening of the left ventricle. As compared to the 219 patients with image quality adequate for strain analysis, the 82 excluded patients were less frequently female (45% vs. 61%), had a lower prevalence of chronic obstructive pulmonary disease (6% vs. 16%), a higher prevalence of diabetes (49% vs. 34%), and a lower LVEF (56% vs. 59%, p= 0.006). No significant differences were noted in other clinical or echocardiographic measures, including age, NT-proBNP level, LV mass index, LAVi, E', and E/E'. (Detailed information on included and excluded patients are given in Online Table S1.) For deformation analysis, endocardial borders were traced at the end-diastolic frame in apical views and at an endsystolic frame in short-axis views. End diastole was defined by the QRS complex or as the frame after mitral valve closure. The software tracks speckles along the endocardial border throughout the cardiac cycle. Peak longitudinal strain (LS) and peak circumferential strain (CS) were computed automatically generating regional data from 6 segments and an average value for each view. For patients in sinus rhythm, analyses were performed on a single cardiac cycle; and for patients in atrial fibrillation, strain values were calculated as the average of 3 cardiac cycles. Peak average LS was measured in the apical 4-chamber and apical 2-chamber views (in 6 segments from each view) and averaged, and peak average CS was obtained from 6 segments measured in the short-axis view at the midpapillary level. All strain analysis on HFpEF, HHD, and normal control subjects were performed by a single investigator. Intraobserver variability for LS and CS was assessed in a sample of 30 randomly selected patients. Coefficient of variation was 6.8% and 8.1% for LS and CS,

respectively. Intraclass correlation coefficients were 0.95 for LS (95% confidence interval: 0.91 to 0.98) and 0.94 for CS (95% confidence interval: 0.91 to 0.98).

Statistical analyses: Descriptive statistics for continuous variables are expressed as mean and standard deviation for normally distributed variables and median and interquartile range for non-normally distributed data. Categorical variables are presented as percentages. Comparison of echocardiographic measures between HFpEF versus HHD and normal controls was performed using Student t tests,Wilcoxon rank-sum tests, or chi-square tests, as appropriate. The relationship between average LS and CS and clinical characteristics, echocardiographic measures, electrocardiographic parameters, and NT-proBNP was assessed using linear regression or nonparametric trend tests. Abnormal LS and CS was defined as >1 SD or >2 SD below the mean value of normal controls. The NT-proBNP was log-transformed due to its skewed distribution. Pearson correlation coefficient was used to assess the relationships between log-transformed NTproBNP and strain measures. Multivariable linear regression was used to determine the relationship between strain measures and NT-proBNP after adjustment for potential confounders. All p values were 2-sided, with $p < 0.05$ used to define statistical significance. Statistical analyses were performed using STATA version 11.2 (Stata Corp., College Station, Texas).

Results

Of 301 patients randomized in the PARAMOUNT study, 219 (73%) had echocardiographic images in appropriate format and of adequate quality for speckle-tracking analysis (Online Table S1). Baseline patient characteristics of the 219 included patients are summarized in Table 1. The average age was 71 ± 9 years, and the majority of patients were female, white, and had a history of hypertension. Half had a history of prior HF hospitalization. In addition to diuretic use (100%), which was a required

inclusion criterion, rates of therapy with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (92%) and beta-blockers (80%) were high. The median NTproBNP level was markedly elevated (894 pg/ml, interquartile range: 526 to 1,457 pg/ml).

Among the normal control group (n = 50), the mean age was 69 ± 7 years, 68% were female, the majority was white, and their mean body mass index was 25.9 ± 3.9 kg/m2. All patients in the control group were free of hypertension, diabetes, hyperlipidemia, smoking, coronary artery disease, and structural or valvular heart disease, and were not taking any cardiovascular medication. Echocardiographic analysis showed normal-sized ventricles, wall thickness, and leftatrial size (LAVi 21.3 ± 5.5 ml/m2). Left ventricular ejection fraction was normal (61 ± 3%), and there was no evidence of diastolic dysfunction (E' lateral: 9.0 ± 2.2). Among the 44 age- and sex-matched HHD patients, the average age was 71 ± 8, 61% were female, the majority was white, and their mean body mass index was 28.5 ± 4.8 kg/m^2. Mean blood pressure was 165/85 mm Hg. Echocardiographic analysis showed normal-sized ventricles (mean leftventricular end-diastolic volume 100 ± 17 ml) with preserved LVEF (mean 56 ± 3%). The LV mass index was 73.5 ± 16.1 g/m^2. By definition, all patients had evidence of diastolic dysfunction with a mean E/E' of 9.4 ± 2.2 andLAVi of 26.6 ± 3.7 ml/m2. (A comprehensive summary of clinical and echocardiographic characteristics of the normal control, the HHD, and the HFpEF group is provided in Online Table S2.) Conventional 2-dimensional and Doppler echocardiographic findings in the overall HFpEF cohort are shown in Table 1. Diastolic dysfunction was present in 95% of patients, with 66% having grade II or III diastolic dysfunction. Median septal E/E' was 14.7 (11.5 ± 18.8) and two-thirds presented with enlarged left atria using a cutoff of 29 ml/m2 (median LAVi 33.9 (26.8 ± 43.0) ml/m^2) (19). Despite the high prevalence of diastolic

abnormalities and signs of increased LV filling pressure, LV volumes, mass, and geometry were normal in most subjects, with only 15% demonstrating LV hypertrophy and 21% demonstrating concentric remodeling or hypertrophy.

HFpEF versus controls. Although global systolic pump function (LVEF) did not differ significantly between the PARAMOUNT study patients and normal controls (59 ± 8% versus 61 ± 3%, respectively; p = 0.09), HFpEF patients demonstrated significantly lower LS andCS (LS, p<0.0001; CS, p<0.0001) (Fig. 1, Table 2). We observed a relationship between LVEF and both LS (Pearson correlation =-0.46, p<0.001) andCS (Pearson correlation=-0.51, p<0.001). However, both LS and CS remained significantly lower among HFpEF patients compared to controls after adjusting for LVEF (p < 0.001 for both LS and CS) (Fig. 1, Table 2) and after excluding subjects with LVEF <55% (p < 0.0001 for LS, p = 0.0002 for CS). Patients with evidence of ischemic heart disease had worse LS and CS as compared to those HFpEF patients without ischemic heart disease. To further investigate the role of ischemic heart disease in the observed differences in LV deformation, we performed a sensitivity analysis excluding all patients with a history of myocardial infarction, coronary artery disease, revascularization procedures, and anginal symptoms, and all patients with an LVEF <55%. In the remaining 91 patients without any evidence of myocardial ischemia and an LVEF <55%, both LS and CS remained significantly lower as compared to controls (HFpEF vs. controls: LS, -15.7 [-18.0 to -13.8] vs. -19.9 [-21.3 to -18.3], p < 0.0001; CS, -24.2 [-29.0 to -20.4] vs. -26.9 [-28.5 to -25.0], p = 0.0007).

HFpEF versus HHD. Compared to HHD, the HFpEF group demonstrated significantly lower LS (p < 0.0001)and CS (p < 0.0001) (Fig. 1, Table 2). Interestingly, when compared to controls, the HHD group demonstrated significantly lower LS (p < 0.0001) but higher CS (p < 0.0001).

Prevalence of abnormal strain in HFpEF. Abnormal LS and CS was present in 66.7% and 40.4% of HFpEF patients, respectively, when abnormal was defined as >2 SD below the mean value of controls (Table 2). In analyses stratified by LVEF (<50%, 50% to 55%, and >55%), the proportion of patients with abnormal LS and CS was greatest in the lowest LVEF category. The LS was more frequently abnormal than the CS, a pattern that held across all LVEF categories (Table 2). The magnitude of impairment in LS was also more prominent than the magnitude of impairment in CS (average relative reduction compared to controls of 27% and 15%, respectively). Longitudinal strain in HFpEF. Worse LS was significantly associated with nonwhite race, a history of HF hospitalization, higher heart rate, ischemic etiology, and lower LVEF (Table 1). No significant association was noted between LS and sex, cardiovascular comorbidities, or pharmacotherapy. Importantly, LS was not associated with systolic or diastolic blood pressure, and 70% of patients with normal blood pressure at the time of echocardiography had abnormal LS. Worse LS was significantly associated with lower LVEF ($p < 0.001$), stroke volume ($p = 0.003$), and S' ($p = 0.009$). The association with LVEF remained significant when LVEF was stratified into categories (LVEF <50%, $p < 0.001$; LVEF 50% to 55%, $p = 0.005$; LVEF >55%, $p < 0.001$) (Table 1). Worse LS was also associated with higher LV end-systolic volume index ($p < 0.001$), LV end-diastolic volume index (p ¼ 0.03), and LV mass index (p ¼ 0.04). There was no association between LS and echocardiographic measures of diastolic function (Table 1).

Circumferential strain in HFpEF. Patients with worse CS were more likely to have a history of HF hospitalization, coronary heart disease, and prior myocardial infarction. Worse CS was also associated with lower systolic blood pressure but not with age, race, or heart rate. Like LS, lower CS was associated with lower LVEF, lower stroke volume, and higher LV end-systolic volume index. The association with LVEF remained

significant after stratification by LVEF category (LVEF <50%, p < 0.001; LVEF 50% to 55%, p ¼ 0.012; LVEF >55%, p < 0.001) (Table 3). There was no association between CS and S' (p =0.40). Similar to LS, there was no association between CS and measures of diastolic function. The CS was related to LV geometry, with worse CS being significantly related to lower RWT (Table 3). Similarly, in a multivariable model accounting for clinical covariates and echocardiographic measures of cardiac structure and function, LV mass index was significantly associated with CS (p = 0.02).

Association of strain and NT-proBNP. Worse LS (modeled both as categorical variable in quartiles and continuously) was associated with higher NT-proBNP levels, both when modeled continuously (Pearson correlation 0.20, p = 0.005) (Fig. 2) and categorically (as quartiles; p for trend = 0.005). The inverse relationship between LS and NT-proBNP remained significant after adjusting for age, sex, systolic and diastolic blood pressure, body mass index, LVEF, LAVi, E/E', atrial fibrillation, and estimated glomerular filtration rate (adjusted p = 0.001). This robust relationship also remained significant when adjusting for E' instead of E/E' (p = 0.001) or when adding E´ (p = 0.001) or S´ (p = 0.002) to the model. In contrast to LS, contemporary measures of diastolic function (E´ and LAVi) were not independently associated with NT-proBNP, nor was a history of ischemic heart disease or presence of EF <55%. The inverse association of LS with NT-proBNP, however, remained significant in the subgroup of patients without ischemic heart disease and with EF ≥55%. The CS was not associated with NT-proBNP.

Discussion

Principal findings. This study of 219 patients with HFpEF enrolled in a contemporary international multicenter clinical trial has 3 major findings. First, LV LS and CS are significantly reduced in HFpEF compared to normal controls and to age- and sex-

matched hypertensive patients with diastolic dysfunction. Second, the prevalence of reduced LS and CS in HFpEF is high. Although LS and CS are significantly related to LVEF, the impairment in LS and CS in HFpEF persists even when restricted to patients with EF >55% or to patients without coronary heart disease. More than half of HFpEF patients with an LVEF _55% had reduced LS. Neither LS nor CS were related to standard echocardiographic measures of diastolic function (E' or E/E'). Third, LS is significantly and independently associated with NT-proBNP level, a prognostically relevant biomarker in HFpEF.

Systolic dysfunction in HFpEF. Although LVEF is the most commonly used and accepted measure of systolic function, it is highly load dependent and relatively insensitive to subtle abnormalities of LV function (8,27). Indeed, some studies involving select HFpEF patients have failed to demonstrate abnormalities in systolic performance, reflected in stroke work, preload recruitable stroke work, and peak (þ)dP/dt (28). In contrast, several other studies evaluating multiple noninvasive measures of LV systolic function by standard echocardiographic techniques, such as LV midwall fractional shortening or mitral annular plane systolic displacement, indicate that systolic function may not be uniformly normal in HFpEF (11,29). The reason for these discrepancies are unclear but may be related to the systolic measures evaluated and differences in the HFpEF patients studied. Early data employing tissue Doppler suggest that longitudinal systolic function may be abnormal despite preserved LVEF in conditions predisposing to HF and in HFpEF (6,11). However, tissue Doppler imaging faces technical limitations including preload and afterload dependence and is limited in its ability to assesses different planes of LV deformation other than longitudinal (30). In addition, prior studies in HFpEF have been largely limited to single-center experiences with small series of select patients (12–15). Speckle-tracking echocardiography is a

relatively new technique, largely independent of angle of incidence, tethering, and cardiac translation, which allows for quantification of myocardial deformation in multiple planes. During systole, the components of LV deformation include longitudinal shortening, radial thickening, and circumferential shortening (31). These planes of deformation are thought to be related to LV myocardial fiber orientation, which is primarily in the longitudinal direction subendocardially and primarily in an oblique orientation subepicardially (32). Our findings demonstrate a high prevalence of impaired LV longitudinal function in HFpEF, even among patients with LVEF >55%, with worse LS significantly related to higher NT-proBNP levels even after adjusting for LVEF and diastolic measures. NT-proBNP is a powerful prognostic discriminator in HFpEF (33). Longitudinal strain predicts outcome in low LVEF patients independent of LVEF (24,25). Whether impaired longitudinal deformation has prognostic significance in HFpEF remains to be determined. Our data further suggest impairment in LV circumferential deformation in HFpEF. Conditions predisposing to HFpEF, such as hypertension or diabetes, are characterized by reduced longitudinal strain but an increase in circumferential function (34–36), which has been proposed as a compensatory mechanism to preserve LVEF (37). Our findings suggest that reduced LV CS partially distinguishes patients with HFpEF from asymptomatic persons with similar comorbidities. This hypothesis is also supported by prior studies demonstrating a progressive decrease of global CS from normal to HFpEF to HFrEF groups even after adjustment for LV end-systolic wall stress (12). The underlying pathophysiology in patients with HFpEF has been commonly believed to involve impairment of diastolic function, with increased passive chamber stiffness (38,39). However, the marked phenotypic and pathophysiologic heterogeneity characterizing this syndrome is now well recognized. Traditional noninvasive markers of diastolic dysfunction are absent in

approximately one-third of patients enrolled in large HFpEF trials (40,41). Indeed, in the PARAMOUNT trial, although the majority of patients demonstrated some echocardiographic findings of diastolic abnormalities at rest, frankly elevated filling pressuredbased on an E/E' ratio ≥15-was present in only 49% of the patients. Similarly, the prevalence of concentric ventricular remodeling was very low. These observations suggest that abnormalities other than concentric hypertrophy and elevated filling pressure (assessed as E/ E' ≥15 at rest) may contribute to the pathogenesis of HFpEF. Our findings of lower LV strain, a measure of LV systolic function that was not correlated with diastolic indices, and its independent association with NT-proBNP suggest a contribution of systolic dysfunction despite preserved LVEF in at least a subset of patients with HFpEF. Study limitations. Strain analysis was not possible in all patients enrolled in the PARAMOUNT trial, although no significant systematic differences were noted between patients included or excluded from this analysis. Studies were performed at 65 sites and on echocardiography machines from a variety of vendors. However, all studies were recorded digitally, and quantitative analysis was performed centrally at a blinded core laboratory. All echocardiograms were performed in a resting condition, which limits the ability to assess the relationship between LS and impaired functional capacity, an important hallmark of the HFpEF syndrome. Patients enrolled in this contemporary HFpEF clinical trial may not be representative of HFpEF patients in the community, because of specific clinical trial inclusion and exclusion criteria. Future studies with clinical outcomes will be essential to understand the clinical relevance of our findings.

Conclusions

Systolic impairment in LV longitudinal and circumferential deformation is prevalent in HFpEF. Worse LS, in particular, is associated with higher NT-proBNP. Our findings

suggest that abnormalities of LV systolic function measured by strain imaging may contribute to the HFpEF syndrome. These findings may help inform future studies to identify pathophysiologically relevant subgroups of patients within this heterogeneous syndrome.

Reprint requests and correspondence: Dr. Scott D. Solomon, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: ssolomon@ rics.bwh.harvard.edu.

REFERENCES

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.

2. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 2005;47:320–32.

3. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13:18–28.

4. Paulus WJ, Tschoepe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.

5. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failuredabnormalities in active relaxation and passive stiffness of the left ventricle.NEngl J Med 2004;350:1953–9.

6. Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002;87:121–5.

7. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with “isolated” diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195–201.

8. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation 2006;113:296–304.

9. Vinereanu D, Lim PO, Frenneaux MP, Fraser AG. Reduced myocardial velocities of left ventricular long-axis contraction identify both systolic and diastolic heart failureda comparison with brain natriuretic peptide. Eur J Heart Fail 2005;7:512–9.
10. Bruch C, Gradaus R, Gunia S, Breithardt G, Wichter T. Doppler tissue analysis of mitral annular velocities: evidence for systolic abnormalities in patients with diastolic heart failure. J Am Soc Echocardiogr 2003;16:1031–6.
11. Petrie MC, Caruana L, Berry C, McMurray JJ. "Diastolic heart failure" or heart failure caused by subtle left ventricular systolic dysfunction? Heart 2002;87:29–31.
12. Yip GW, Zhang Q, Xie JM, et al. Resting global and regional left ventricular contractility in patients with heart failure and normal ejection fraction: insights from speckle-tracking echocardiography. Heart 2011;97:287–94.
13. Carluccio E, Biagioli P, Alunni G, et al. Advantages of deformation indices over systolic velocities in assessment of longitudinal systolic function in patients with heart failure and normal ejection fraction. Eur J Heart Fail 2011;13:292–302.
14. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36–46.
15. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008;29:1283–9.
16. Solomon SD, Zile M, Pieske B, et al., for the Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696

in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387–95.

17. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. J Am Soc Echocardiogr 2005;18: 1440–63.

18. Solomon SD, Verma A, Desai A, et al. Effect of intensive versus standard blood pressure lowering on diastolic function in patients with uncontrolled hypertension and diastolic dysfunction. Hypertension 2010;55:241–8.

19. Hassanein A, Desai A, Verma A, et al. EXCEED: Exforge-Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction: study rationale, design, and participant characteristics. Ther Adv Cardiovasc Dis 2009;3:429–39.

20. Solomon SD, Foster E, Bourgoun M, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: MADIT-CRT. Circulation 2010;122:985–92.

21. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

22. Amundsen BH, Helle-Velle T, Edvardsen T, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789–93.

23. Pirat B, Khoury DS, Hartley CJ, et al. A novel feature-tracking echocardiographic method for the quantification of regional myocardial function: validation in an animal model of ischemia-reperfusion. J Am Coll Cardiol 2008;51:651–9.

24. Shin SH, Hung CL, Uno H, et al. Mechanical dyssynchrony after myocardial infarction in patients with left ventricular dysfunction, heart failure, or both. Circulation 2010;121:1096–103.

25. Hung CL, Verma A, Uno H, et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. J Am Coll Cardiol 2010;56:1812–22.

26. Knappe D, Pouleur AC, Shah AM, et al. Dyssynchrony, contractile function, and response to cardiac resynchronization therapy. Circ Heart Fail 2011;4:433–40.

27. Carabello BA. Evolution of the study of left ventricular function: everything old is new again. Circulation 2002;105:2701–3.

28. Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation 2005;111:2306–12.

29. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. J Am Coll Cardiol 2009;54:410–8.

30. Yu CM, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging: a new prognosticator for cardiovascular diseases. J Am Coll Cardiol 2007;49:1903–14.

31. Shah AM, Solomon SD. Myocardial deformation imaging: current status and future directions. Circulation 2012;125:244–8.

32. Buckberg G, Mahajan A, Saleh S, Hoffman JI, Coghlan C. Structure and function relationships of the helical ventricular myocardial band. J Thorac Cardiovasc Surg 2008;136:578–89.

33. Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. Circ Heart Fail 2011;4:569–77.

34. Mizuguchi Y, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Oki T. The functional role of longitudinal, circumferential, and radial myocardial deformation for regulating the early impairment of left ventricular contraction and relaxation in patients with cardiovascular risk factors: a study with two-dimensional strain imaging. J Am Soc Echocardiogr 2008;21:1138–44.

35. Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. Clin Sci (Lond) 2004;106:53–60.

36. Imbalzano E, Zito C, Carerj S, et al. Left ventricular function in hypertension: new insight by speckle tracking echocardiography. Echocardiography 2011;28:649–57.

37. Shah AM, Solomon SD. Phenotypic and pathophysiological heterogeneity in heart failure with preserved ejection fraction. Eur Heart J 2012;33:1716–7.

38. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 2011;32:670–9.

39. Westermann D, Kasner M, Steendijk P, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation 2008; 117:2051–60.

40. Persson H, Lonn E, Edner M, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic SubstudydCHARMES. J Am Coll Cardiol 2007;49:687–94.

41. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation 2011;124: 2491–501.

Key Words: cardiac biomarkers - diastolic heart failure - echocardiography - mechanics - systolic strain.

Tables

Table 1- Baseline Characteristics According to Quartiles of Longitudinal Strain

	Overall (n = 219)	LS Quartile 1 (n = 55)	LS Quartile 2 (n = 55)	LS Quartile 3 (n = 55)	LS Quartile 4 (n = 54)	p Value for Trend
Longitudinal strain, %	−14.6 ± 3.3	−26.5 to −16.5	−16.4 to −14.8	−14.8 to −12.3	−12.2 to −7.4	
Clinical characteristics						
Age	72 (66–78)	70 (66–76)	74 (70–80)	73 (66–79)	70 (60–78)	0.226
Female	61	67	53	64	59	0.86
White race	83	93	85	89	65	<0.001
Medical history						
Hypertension	90	91	93	95	90	0.97
Diabetes mellitus	34	33	33	24	48	0.22
Renal disease, eGFR<60 ml/kg/1.73 m^2	37	38	36	45	28	0.51
Coronary heart disease	42	27	51	47	44	0.11
Prior MI	19	13	27	16	21	0.55
Prior HF hospitalization	50	36	49	53	63	0.006
Systolic BP, mm Hg	136 (128–145)	139 (127–146)	139 (130–147)	136 (124–150)	132 (128–140)	0.46
Diastolic BP, mm Hg	80 (71–84)	75 (68–85)	78 (73–85)	80 (72–82)	80 (75–82)	0.12
Body mass index, kg/m^2	29.7 (26.1–33.6)	30.9 (27.2–34.0)	29.1 (25.8–32.9)	29.8 (26.1–36.8)	27.5 (24.6–31.7)	0.03
Body surface area, m^2	1.85 (1.68–2.00)	1.90 (1.72–2.03)	1.85 (1.73–1.96)	1.83 (1.70–2.07)	1.75 (1.61–1.95)	0.022
Electrocardiogram						
Heart rate, beats/min	66 (60–75)	62 (58–73)	64 (55–74)	68 (60–75)	71 (64–81)	0.001
LBBB	5	2	4	7	9	0.06
Atrial fibrillation	29	35	35	24	22	0.08
Biomarkers						
NT-proBNP, pg/ml	894 (526–1,457)	771 (419–1,036)	946 (540–1,454)	999 (582–1,615)	941 (663–2,119)	0.005
Echocardiographic characteristics						
LV structure						
LVEDVi, ml/m^2	58.4 (50.5–67.9)	55.4 (49.4–64.8)	58.6 (50.5–73.0)	57.4 (50.8–66.3)	63.3 (54.6–72.7)	0.034
LVESVi, ml/m^2	23.2 (19.1–29.6)	20.5 (16.8–24.6)	22.8 (19.9–30.6)	24.5 (18.1–28.8)	28.7 (22.4–34.3)	<0.001
RWT	0.37 (0.33–0.40)	0.37 (0.34–0.41)	0.37 (0.33–0.42)	0.36 (0.32–0.40)	0.36 (0.32–0.40)	0.12
LVMi, g/m^2	74.1 (63.2–90.7)	71.0 (60.0–85.8)	75.4 (62.3–95.1)	73.0 (63.2–84.5)	81.1 (66.8–96.0)	0.036
Concentric remodeling, %	13	15	11	13	14	0.92
Concentric hypertrophy, %	8	9	13	4	6	0.24
Eccentric hypertrophy, %	7	4	11	4	10	0.51
Systolic function						
LVEF, %	59.2 (53.7–63.6)	63.3 (58.9–67.0)	59.8 (54.1–62.2)	58.1 (53.5–62.7)	54.0 (49.6–59.3)	<0.001
LVEF <50%	11	0	5	11	26	<0.001
LVEF 50%–55%	22	11	20	22	34	0.005
LVEF >55%	68	89	75	67	40	<0.001
LV stroke volume, ml	61.4 (52.6–76.5)	66.4 (53.7–82.9)	67.7 (54.6–79.7)	60.5 (51.9–71.7)	59.2 (50.3–71.2)	0.003
S' mean, cm/s	6.29 (5.24–7.21)	6.51 (5.86–7.66)	6.34 (5.33–7.04)	5.61 (4.96–6.69)	6.25 (4.88–7.24)	0.009
Diastolic function						
E' lateral, cm/s	7.4 (5.4–9.0)	7.3 (5.2–9.4)	7.4 (5.8–8.9)	7.1 (5.3–8.8)	7.5 (5.4–9.2)	0.94
E' septal, cm/s	5.3 (4.2–6.8)	5.4 (4.4–6.6)	5.2 (4.5–6.8)	5.2 (4.0–7.4)	5.4 (4.2–6.8)	0.64
E/E' ratio (septal)	14.7 (11.5–18.8)	15.7 (12.1–19.1)	14.2 (11.1–18.1)	14.2 (11.4–20.1)	15.3 (11.5–22.6)	0.84
LAVi, ml/m^2	33.9 (26.8–43.0)	34.2 (27.9–45.0)	35.1 (28.1–44.7)	31.5 (24.0–41.2)	34.1 (27.4–40.5)	0.49

Values are mean _ SD, median (interquartile range), or n. The p value for trend across quartiles of longitudinal strain (LS) is averaged from apical 4- and 2-chamber views. BP = blood pressure; E/E' ratio = mitral inflow to mitral relaxation velocity ratio; eGFR = estimated glomerular filtration rate; E' lateral = lateral mitral relaxation velocity; E' septal = septal mitral relaxation velocity; HF= heart failure; LAVi = left atrial volume index; LBBB = left bundle branch block; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi =left ventricular end-systolic volume index; LVMi = left ventricular mass index; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; RWT = relative wall thickness.

Table 2 Percentage of Patients With Abnormal Strain

	Controls	HHD	HFpEF Overall	HFpEF by LVEF Category			p Value (HHD vs. Control)	p Value (HFpEF vs. Control)	p Value (HFpEF vs. HHD)
				EF <50%	EF 50%–55%	EF >55%			
Longitudinal strain	n = 50	n = 44	n = 219	n = 23	n = 47	n = 149			
Mean ± SD, %	−20.0 ± 2.1	−17.07 ± 2.04	−14.6 ± 3.3	11.5 ± 2.5	−13.5 ± 3.1	−16.6 ± 3.5	<0.0001	<0.0001†	<0.0001
Percent abnormal									
>1 SD below normal (−17.9)		61.4%	71%	100%	92%	64%			
>2 SD below normal (−15.8)		29.6%	54.3%	100%	81%	43%			
Circumferential strain	n = 50	n = 41	n = 146	n = 14	n = 35	142			
Mean ± SD, %	−27.1 ± 3.1	−30.1 ± 3.5	−22.9 ± 5.9	16.9 ± 4.0	−21.0 ± 4.1	−25.3.5 ± 4	<0.0001	<0.0001†	<0.0001
Percent abnormal									
>1 SD below normal (−24)		2.4%	51%	100%	71%	42%			
>2 SD below normal (−20.9)		0%	31%	79%	54%	20%			

*> 1 or 2 standard deviations from the mean value for normal controls. † $p < 0.001$ when adjusted for left ventricular ejection fraction (LVEF). EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; HHD = hypertensive heart disease

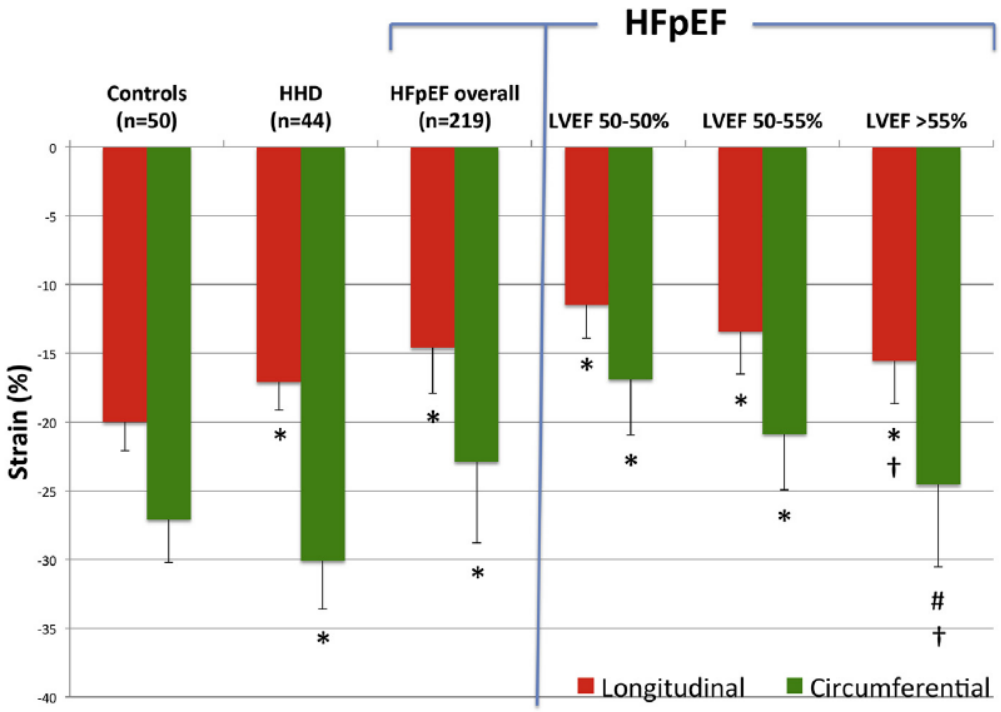
Table 3 Baseline Characteristics According to Quartiles of Circumferential Strain

	Overall (n = 146)	CS Quartile 1 (n = 37)	CS Quartile 2 (n = 36)	CS Quartile 3 (n = 38)	CS Quartile 4 (n = 35)	p Value for trend
Circumferential strain, %	−22.9 ± 5.9	−40.9 to −25.9	−25.9 to −22.1	−22.1 to −18.9	−18.9 to −11.1	
Clinical characteristics						
Age	73 (66–79)	74 (67–78)	71 (64–79)	74 (66–78)	72 (66–79)	0.71
Female	62	59	75	63	49	0.24
White race	84	92	75	84	83	0.51
Medical history						
Hypertension	90	95	89	89	88	0.40
Diabetes mellitus	37	35	36	37	41	0.61
Renal disease, eGFR<60 ml/kg/1.73 m^2	35	39	19	38	43	0.40
Coronary heart disease	38	30	25	40	59	0.006
Prior MI	17	5	17	16	32	0.005
Prior HF hospitalization	51	27	53	58	66	0.001
Systolic BP, mm Hg	134 (127–144)	140 (132–147)	135 (130–150)	127 (120–140)	133 (128–140)	0.03
Diastolic BP, mm Hg	80 (70–84)	78 (74–85)	80 (70–88)	78 (70–80)	79 (70–83)	0.88
Body mass index, kg/m^2	29.9 (25.8–33.6)	30.0 (26.5–34.0)	28.4 (24.3–32.0)	30.9 (26.3–34.5)	30.1 (25.6–32.7)	0.81
Body surface area, m^2	1.86 (1.68–2.02)	1.94 (1.72–2.09)	1.75 (1.67–1.95)	1.85 (1.75–1.99)	1.88 (1.66–2.03)	0.74
Electrocardiogram						
Heart rate, beats/min	66 (60–75)	63 (59–72)	69 (61–77)	67 (60–75)	68 (60–75)	0.14
Atrial fibrillation	32	30	39	29	31	0.89
Biomarkers						
NT-proBNP, pg/ml	945 (513–1,561)	1,036 (540–1,834)	833 (457–1,495)	836 (482–1,459)	951 (726–1,796)	0.86
Echocardiographic characteristics						
LV structure						
LVEDVi, ml/m^2	58.4 (50.7–67.6)	56.5 (49.6–65.1)	58.3 (53.5–68.2)	58.4 (47.9–66.0)	61.5 (50.9–73.8)	0.48
LVESVi, ml/m^2	22.9 (19.0–29.4)	20.3 (16.6–24.9)	24.1 (20.0–30.8)	22.6 (19.0–28.9)	28.2 (22.1–35.1)	0.001
RWT	0.36 (0.33–0.41)	0.37 (0.35–0.43)	0.39 (0.34–0.42)	0.35 (0.33–0.40)	0.34 (0.32–0.39)	0.016
LVMi, g/m^2	73.8 (62.1–90.6)	73.8 (58.3–91.8)	73.6 (63.3–86.5)	71.8 (62.2–90.6)	75.0 (65.1–90.7)	0.79
Concentric remodeling, %	15	14	23	11	12	0.53
Concentric hypertrophy, %	8	14	6	3	9	0.37
Eccentric hypertrophy, %	7	8	6	8	6	0.83
Systolic function						
LVEF, %	59.9 (53.7–64.1)	63.1 (60.5–67.1)	59.1 (54.3–64.3)	59.3 (53.3–62.6)	54.2 (49.6–60.3)	<0.001
LVEF <50%	8	0	6	3	27	<0.001
LVEF 50%–55%	24	11	20	32	33	0.014
LVEF >55%	68	89	74	65	39	<0.001
LV stroke volume, ml	61.1 (52.1–78.4)	68.3 (57.7–85.2)	59.7 (55.1–73.1)	61.5 (51.1, 73.2)	56.6 (47.6, 75.7)	0.02
S' mean, cm/s	6.17 (5.21–7.07)	6.22 (5.49–7.30)	6.11 (5.24–6.91)	6.49 (5.24, 7.21)	5.83 (4.89, 7.35)	0.40
Diastolic function						
E' lateral, cm/s	7.1 (5.1–8.8)	7.0 (5.4–8.7)	7.0 (4.6–10.2)	7.2 (5.2–8.3)	7.4 (5.4–9.4)	0.70
E' septal, cm/s	5.3 (4.2–7.1)	5.3 (4.3–6.3)	5.2 (4.2–7.4)	5.1 (4.2–7.1)	6.0 (4.0–7.6)	0.88
E/E' ratio (septal)	14.8 (11.7–19.1)	14.2 (11.2–18.3)	13.8 (11.4–19.0)	15.8 (13.1–22.4)	14.2 (11.7–19.0)	0.55
LAVi, ml/m^2	34.4 (27.7–44.1)	33.7 (28.8–45.0)	38.2 (28.1–46.8)	36.5 (28.4–40.9)	33.4 (24.4–44.1)	0.60

Values are mean ± SD, median (interquartile range), or n. The p value for trend across quartiles of CS (circumferential strain) is from the parasternal short-axis view. Abbreviations as in Table 1.

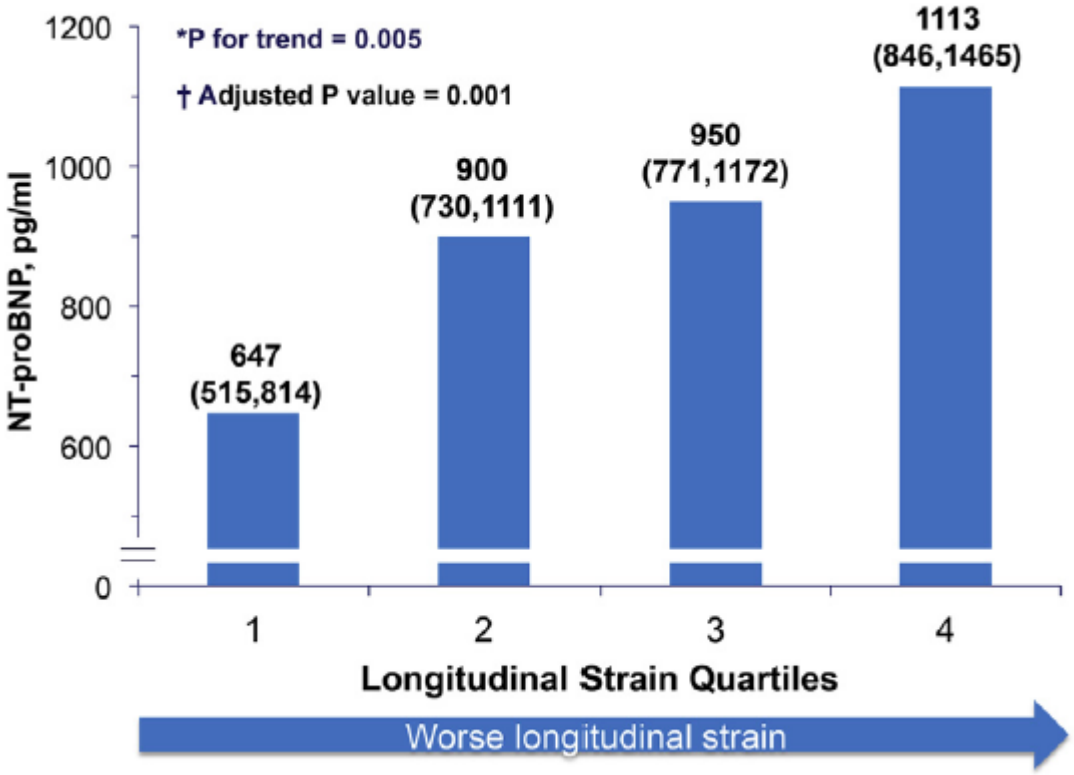
Figures

Figure 1: Average Longitudinal and Circumferential Systolic Strain



Average longitudinal strain (red bars) and circumferential systolic strain (green bars) among normal controls (n = 50), hypertensive heart disease (HHD) patients (n = 44), heart failure with preserved ejection fraction (HFpEF) patients overall (n = 219), and in 3 categories HFpEF based on left ventricular ejection fraction (LVEF). *$p < 0.0001$ compared to controls and between HHD and HFpEF overall for longitudinal strain and circumferential strain. #$p = 0.0002$ compared to controls. †LVEF-adjusted $p < 0.001$ compared to controls.

Figure 2 Association of Longitudinal Systolic Strain and NT-proBNP.



Association of longitudinal systolic strain (quartiles) and N-terminal pro-brain natriuretic peptide (NT-proBNP), geometric means and 95% confidence intervals. *Trend test performed using log-transformed NT-proBNP data. †Analysis adjusted for age, sex, systolic and diastolic blood pressure, body mass index, E/E', left ventricular ejection fraction, left atrial volume index, atrial fibrillation, and estimated glomerular filtration rate.

APPENDIX

Online Table S1:

Comparison of PARAMOUNT patients included versus excluded into the speckle tracking analysis

Variable	Included (n = 219)	Excluded (n = 82)	p Value
Age	72 (66, 78)	71 (66, 78)	0.83
Female, %	61	45	0.02
White, %	83	46	<0.001
Hypertension, %	92	98	0.11
DM, %	34	49	0.02
Renal disease, %	44	36	0.24
CHD, %	42	45	0.70
MI, %	19	24	0.34
Stroke, %	6	4	0.58
COPD, %	16	6	0.02
Heart rate	66 (60, 75)	70 (60, 79)	0.02
ECG AF, %	29	27	0.78
NT-pro BNP	894 (526, 1457)	693 (388, 1273)	0.10
Systolic BP, mmHg	135 (129, 144)	131 (125, 141)	0.01
Diastolic BP, mmHg	78 (71, 83)	78 (70, 82)	0.82
BMI, kg/m^2	29.7 (26.1, 33.6)	28.5 (25.9, 31.8)	0.17
LVEDVI, ml/m^2	58.3 (50.4, 67.7)	59.1 (52.1, 73.6)	0.31
LVESVI, ml/m^2	23.0 (19.0, 29.0)	27.4 (21.1, 33.7)	0.03

RWT	0.37 (0.33, 0.40)	0.37 (0.31, 0.41)	0.71
LVMI, g/m^2	73.8 (63.2, 90.6)	81.8 (69.6, 91.7)	0.14
LVEF, %	59.2 (53.9, 63.6)	55.5 (49.6, 61.3)	0.006
Stroke volume, ml	61.4 (52.7, 76.5)	61.6 (54.5, 72.8)	0.90
E/E’	14.6 (11.5, 18.5)	13.5 (8.8, 17.5)	0.10
E’lateral, cm/sec	7.4 (5.3, 9.0)	7.6 (5.9, 10.6)	0.23
LAVI, ml/m^2	33.5 (26.5, 43.0)	34.0 (24.5, 40.6)	0.80

*Data presented as median (IQR), p for comparison of included versus excluded.

Online Table S2:

Clinical and echocardiographic characteristics of normal controls, HHD and HFpEF

	Controls (n = 50)	**HHD (n = 44)**	**HFpEF (n = 219)**
Age	69±7	71 ±8	71±9
Female, %	68	61	61
Hypertension, %	0	100	92
Diabetes, %	0	2	34
Renal disease, %	0	16	37
CHD, %	0	9	42
MI, %	0	NA	19
Systolic BP, mm Hg	130 (118, 138)	163 (154, 172)	136 (128, 145)
Diastolic BP, mm Hg	74 (68, 84)	87 (78, 92)	80 (71, 84)
BMI, kg/m^2	26.3 (22.1, 28.2)	27.4 (26.0, 31.3)	29.7 (26.1, 33.6)
BSA	1.75 (1.66, 1.89)	1.81 (1.72, 2.0)	1.85 (1.68, 2-0)
HR, bpm	69.5 (62.5, 76.5)	NA	66 (60, 75)
LVEF, %	61±3	56±3	59±8
LVEDVI, ml/m^2	44.5 (39.2, 54.4)	52.9 (47.4, 59.7)	58.4 (50.5, 67.9)
LAVi, ml/m^2	20.2 (17.9, 24.8)	26.7 (23.6, 29.3)	33.9 (26.8, 43.0)
E' lateral, cm/sec	9 (7.7, 10.7)	7.5 (6.6, 7.9)	7.4 (5.4, 9)

*Values presented as % for categorical variables and median (IQR) or mean ± SD for continuous variables.

Artigo 3

Impaired Left Atrial Function in Heart Failure with Preserved Ejection Fraction

Angela B. S. Santos[1,2*]; Elisabeth Kraigher-Krainer[1,3*]; Deepak K. Gupta[1]; Brian Claggett[1]; Michael R. Zile[4]; Burkert Pieske[3]; Adriaan A. Voors[5]; Marty Lefkowitz[6]; Toni Bransford[6]; Victor Shi[6]; Milton Packer[7]; John J. V. McMurray[8]; Amil M. Shah[1], Scott D. Solomon[1] for the PARAMOUNT Investigators

From [1]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA; [2]Postgraduate Program in Cardiovascular Sciences, Cardiology, Federal University of Rio Grande do Sul, BR; [3]Medical University Graz, Graz, Austria; [4]RHJ Department of Veterans Affairs Medical Center and Medical University of South Carolina, Charleston, SC, USA; [5]University of Groningen, Groningen, The Netherlands; [6]Novartis Pharmaceuticals, East Hanover, NJ, USA; [7]University of Texas Southwestern, Dallas, TX, USA; [8]University of Glasgow, Glasgow, UK

Correspondence to Scott D. Solomon, MD, Cardiovascular Division, Brigham and Women's Hospital; 75 Francis St, Boston, MA 02445; Tel: 857-307-1960/ Fax: 857-307-1944; E-mail ssolomon@rics.bwh.harvard.edu

*Both authors contributed equally to this article.

Abstract

Aims: Left atrial (LA) enlargement is present in the majority of heart failure with preserved ejection fraction (HFpEF) patients and is a marker of risk. However, the importance of LA function in HFpEF is less well understood.

Methods and Results: The PARAMOUNT trial enrolled HFpEF patients (LVEF ≥ 45%, NT-proBNP > 400 pg/ml). We assessed LA reservoir, conduit and pump function using 2D volume indices and speckle tracking echocardiography in 135 HFpEF patients in sinus rhythm at the time of echocardiography and 40 healthy controls of similar age and gender. LA strain was related to clinical characteristics and measures of cardiac structure and function. Compared to controls, HFpEF patients had worse LA reservoir, conduit, and pump function. The differences in systolic LA strain (Controls, 39.2 ± 6.6% vs HFpEF, 24.6 ± 7.3%) between groups remained significant after adjustments and even in the subsets of HFpEF patients with normal LA size or without a history of AF. Among HFpEF patients, lower LA strain was associated with higher prevalence of prior HF hospitalization and history of AF, as well as worse LV systolic function, higher LV mass and LA volume. However, NT-proBNP and E/E' were similar across the quartiles of LA function.

Conclusions: In this HFpEF cohort, we observed impairment in all phases of LA function, and LA strain was decreased independent of LA size or history of AF. LA dysfunction may be a marker of severity and play a pathophysiologic role in HFpEF.

Clinical Trial Registration: (Clinicaltrials.gov NCT00887588)

Key words: Diastolic Heart Failure; Echocardiography; Atrial Strain

Introduction

Heart failure with preserved ejection fraction (HFpEF) is common,[1,2] particularly among elderly, female, and hypertensive patients, and is frequently associated with atrial fibrillation.[3,4] This condition is also associated with increased mortality and hospital readmission.[5,6] The pathophysiologic mechanisms underlying HFpEF are heterogeneous and incompletely understood. Traditionally, HFpEF has been attributed to abnormal left ventricular (LV) diastolic function, including abnormalities in active relaxation and passive stiffness.[7,8] Left atrial (LA) enlargement is a recognized marker for LV diastolic function and is independently associated with an increased risk for morbidity and mortality.[9-11] While increased LA size is present in the majority of HFpEF patients, approximately one-third do not have LA enlargement.[10,12] The role of all 3 phases of LA function in HFpEF patients is less well understood,[13,14] particularly in those without a history of atrial fibrillation (AF) and with normal LA size.

We used baseline data from the The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) Trial, a large well-phenotyped cohort of HFpEF patients, to test the hypothesis that LA function is abnormal in HFpEF patients, even among patients without LA enlargement or history of AF. We also sought to determine the clinical and echocardiographic correlates of reduced LA strain in patients with HFpEF.

Methods

Study Population

The PARAMOUNT trial (Clinicaltrials.gov NCT00887588) recruited patients between Nov, 2009 and March, 2011 and was undertaken in 65 centers and 13 countries. The trial enrolled men and women over 40 years of age, with LV ejection fraction (LVEF) $\geq$45%, documented history of heart failure with NYHA class II-IV symptoms, and NT-proBNP levels >400 pg/mL at the baseline visit.[15] Patients were excluded if they had a previous LVEF less than 45% at any time, isolated right heart failure due to pulmonary diseases, dyspnea due to non-cardiac causes such as pulmonary diseases, anemia or severe obesity, primary valvular, coronary or cerebrovascular disease. The number of patients enrolled with AF was limited to approximately 25% of the total sample, checked by ECG at screening. Of the 301 patients enrolled in the PARAMOUNT trial, 135 patients were in sinus rhythm (SR) at the time of echocardiography and had image quality sufficient for LA speckle tracking analysis (excluded patients: 75 in AF at the time of echocardiography; 47 non-DICOM images; 44 missing view(s) and/or unsuitable images for LA speckle tracking analysis). Among the 135 included patients, 32 self-reported a history of AF and/or were in AF according to the screening ECG (performed one week before the echocardiogram), but were in SR at the time of echocardiography.

A group of 40 healthy controls was retrospectively identified from the medical records of the Brigham and Women's Hospital (BWH). The search strategy targeted patients >55 years who had an echocardiogram, and no ICD-9 code in their record for any of the following conditions: hypertension, ischemic heart disease, cardiac arrhythmia, hypercholesterolemia, chronic obstructive lung disease, diabetes mellitus, cerebrovascular disease, arterial vascular disease, and cancer. This group was further

selected to have normal LVEF, no LV regional motion abnormalities, normally sized cardiac chambers, no significant valvular disease and suitable echocardiogram image quality. Controls were of a similar age and gender distribution to the HFpEF group. Our final control sample was achieved from an initial search including 2,000 patients. The study protocol was approved by the BWH Institutional Review Board.

Echocardiographic Analyses

Standard echocardiographic and Doppler parameters were analyzed using an offline analysis workstation at the Cardiovascular Imaging Core Lab at BWH, Boston, MA. All pre-specified measurements in the PARAMOUNT trial were made in triplicate in accordance with the recommendations of the American Society of Echocardiography [16,17] and included LA and LV diameter and volumes, LV wall thickness, LV mass, LVEF, mitral inflow propagation and lateral mitral annular relaxation velocities.

LA and LV function indices were measured using B-mode speckle-tracking vendor-independent software with algorithms designed for the LV (TomTec Imaging Systems, Unterschleissheim, Germany) that is angle independent and identifies cardiac motion by tracking multiple reference points over time.[18,19] The LA and LV endocardial borders were traced at the end-diastolic frame of 2D images acquired from the 12 segments using apical 2- and 4-chamber views.[18] The PARAMOUNT echocardiography protocol required the proper alignment of apical views, in order to capture the LA in full, avoiding foreshortening of the chamber and to maintain a frame rate of 50-80 frames per second during the acquisition. End-diastole was defined by the QRS complex or as the frame after mitral valve closure. Speckles were tracked frame by frame throughout the

LA and LV myocardium over the course of one cardiac cycle; basal, mid, and apical regions of interest were then created. Semi-quantitative segment tracking was carefully inspected for each image and manually adjusted as needed. If more than 2 segments could not be tracked or there was a lack of a full cardiac cycle or significant foreshortening of the cavity, the measurements were considered unreliable and the patient was excluded from the analysis. For LV function analysis, global longitudinal strain was calculated as the average LV longitudinal strain across the apical 4- and 2-chamber views.[20] From LA speckle tracking analysis, LA phasic function was estimated using volumes and strain indices calculated as the average across the apical 4- and 2-chamber views. LA volumes versus time curves were generated by calculating LA volume at each phase of the cardiac cycle (LA maximal, LA pre-A, and LA minimum volumes) using the single-plane Simpson's method (Figure 1-left panel). From LA volumes, LA phasic function was estimated as:

- LA emptying fraction (reservoir function) = [(LA maximum volume – LA minimal volume)/LA maximum volume]*100.
- LA passive emptying fraction (conduit function) = [(LA maximum volume – LA pre-A volume)/LA maximum volume]*100

  LA active emptying fraction (pump function) = [(LA pre-A volume – LA minimal volume)/LA pre-A volume]*100

Also LA reservoir function was estimated as LA expansion index (LA maximum volume – LA minimal volume)/LA minimal volume]*100. From LA strain analysis, LA phasic function was estimated using: peak strain during systole (systolic LA strain) to assess reservoir function, early peak strain rate during diastole (LA passive strain rate) to assess

conduit function, and late peak strain rate during diastole (LA active strain rate) to assess pump function (Figure 1-middle and right panel). All strain analysis on HFpEF patients and normal controls were performed by a single investigator.

Intra-observer variability for LA strain was assessed in 20 randomly selected PARAMOUNT studies: coefficient of variation was 6.3% and intraclass correlation coefficient was 0.86 (95% CI 0.75-0.98).

Statistical analysis

All normally distributed data were presented as mean and standard deviation (continuous data) or as count and proportion (categorical data). Since NT-proBNP distribution was skewed, it was displayed as median and interquartile range and was log-transformed for analysis. Comparisons between groups were assessed using two- sample *t* test with unequal variance or ANOVA (followed by Bonferroni correction) and χ^2 test. After univariate screening, multivariable regression models were used to adjust for selected clinically and statistically significant covariates (age, gender, heart rate, systolic blood pressure, body mass index, left atrial volume index (LAVi), and LV global longitudinal strain and E/E').

Additionally, we categorized the HFpEF patients according to quartiles of LA strain, and applied trend tests across ordered groups to assess the association between LA dysfunction and demographic characteristics and echocardiographic measures of cardiac structure and function. All statistical analyses were performed with STATA 12.0 (Stata Corp, College Station, Texas). All tests were two-sided and p-values of <0.05 were considered statistically significant.

Results

Clinical characteristics

Patients with HFpEF were elderly, more frequently Caucasian (81%), female and overweight. Most (92%) had arterial hypertension, but blood pressure was well controlled (Table 1). All patients were using diuretics (inclusion criteria) and the majority of those patients were using ACE inhibitor or ARB (93%) and b-blocker (81%). As compared to the excluded HFpEF patients, the HFpEF patients included in this analysis had higher systolic blood pressure (139±15mmHg vs 133±14mmHg, p<0.001), slightly higher LV ejection fraction (59 ± 7% vs. 57± 8%, p=0.04) and filling pressure (E/E': 13.7 ± 8.6 vs 11.7 ± 6.0, p=0.04). Also, fewer of the patients included had a history of AF (23% vs 56%, p<0.001), they had a lower heart rate (66 ± 13 vs 72 ±12, <0.001), and smaller LAVi (33.4 ± 11.5 vs 38.1 ± 14.8, p=0.004) than patients not included, likely due to the exclusion of patients with AF at the time of echocardiography.

Compared to controls, patients with HFpEF had similar LVEF, but lower LV global longitudinal strain. HFpEF patients also had higher LV and LA volumes, lower mitral annular relaxation velocities (E' and A') and higher E/E' compared to controls. There was no difference in LV mass between groups, even after adjusting for height$^{2.7}$. The relative wall thickness was higher in controls than in HFpEF patients, which was driven by larger LV end diastolic diameter in the HFpEF group (Table 1). The elevated NT-proBNP, as inclusion criteria in the PARAMOUNT trial, can favor patients with larger left ventricles. Indeed, in our study, LV end diastolic diameter was significantly associated with NT-proBNP levels (p=0.04).

LA function

LA reservoir (systolic LA strain and LA emptying fraction), LA conduit (LA passive strain rate), and LA pump (LA active strain rate and LA active emptying fraction) function were significantly lower in HFpEF patients than in controls. Also, LA expansion index (another measurement of LA reservoir function) was significantly lower in our HFpEF patients than in controls (114.4 ± 7.6 in HFpEF versus 158.8 ± 11.1 in controls, p=0.002). The difference in LA reservoir function (measured by systolic LA strain) between groups remained significant even after adjustment for age, gender, heart rate, systolic blood pressure, BMI, LAVi, LV global longitudinal strain and E/E'(Figure 2). As compared to controls, LA strain was lower even in the subset of HFpEF patients with normal LAVi (n=52) ($\leq$29ml/m^2) [16] (Figure 3) and in the subset of HFpEF patients without known history of AF (n=103) (Figure 4).

Among patients with HFpEF (n=135), those with lower systolic LA strain had a higher prevalence of prior heart failure hospitalization, and history of AF, as well as worse LV systolic function (measured by LVEF and LV global longitudinal strain), higher LV mass and LAVi, when compared to patients with higher LA strain. However, NTproBNP levels and E/E' were similar across the quartiles of LA function (Table 2).

Discussion

We found that HFpEF patients had lower LA reservoir, conduit, and pump function than healthy controls. LA reservoir function (measured by systolic LA strain) remained significantly lower in the HFpEF group, even after adjustment for potential confounders. LA reservoir dysfunction (measured by systolic LA strain) was also present in HFpEF patients despite normal LA size and even among those without a known history of AF. In HFpEF patients, lower systolic LA strain was associated with higher

prevalence of prior heart failure hospitalization and history of AF, as well as lower LV ejection fraction and global longitudinal strain, higher LV mass and LAVi. These findings suggest that LA dysfunction is prevalent in HFpEF and may contribute to its pathophysiology.

LA dysfunction has previously been described in HFpEF patients.[14,21,22] Kurt *et al* demonstrated lower LA reservoir and pump function in a small sample (n=20) of HFpEF patients as compared with healthy controls.[23] In another 2D speckle tracking study of 119 HFpEF patients, LA reservoir and pump function were significantly more impaired in HFpEF patients compared with asymptomatic patients with diastolic dysfunction.[13] LA function estimated by strain analysis using speckle tracking is a direct measurement of intrinsic LA myocardial deformation that is relatively independent of loading conditions and geometric assumptions.[24,25] Moreover, LA strain by speckle tracking has high feasibility and reproducibility.[18] Our results in a relatively large well-defined HFpEF group corroborate these prior studies and extend the findings of LA dysfunction to all 3 phases of LA function (reservoir, conduit and pump function) that may reflect an advanced stage of this syndrome. Further, we found that LA strain was the more robust measure of LA dysfunction in HFpEF patients in that it remained significantly different from controls even after multivariable adjustments and in the subsets with normal LA volume or without prior AF. These findings suggest that LA dysfunction may occur in HFpEF patients independent of LA dilation or remodeling caused by AF. However, due to the cross-sectional nature of this study we cannot conclusively discern whether early LA dysfunction is a consequence of HFpEF, or if LA dysfunction is a mechanism that contributes to an increased susceptibility to HFpEF.

We also found that lower LA reservoir function as assessed by systolic LA strain was associated with a higher prevalence of prior heart failure hospitalization and history of AF. Previous studies showed that impaired LA function was a predictor of HF hospitalization in patients with HF with reduced ejection fraction [26] and among patients with coronary disease and preserved ejection fraction.[27] Moreover, LA dysfunction has been described in AF patients, even in paroxysmal AF during sinus rhythm, [28] which may be attributable to LA wall fibrosis.[29] Worse systolic LA function may also contribute to increased incidence of AF in HFpEF patients.[4] We also observed that lower systolic LA strain was related to worse LV systolic function, greater LV hypertrophy and LA structural remodeling. Impaired LV longitudinal strain has been associated with worse systolic LA strain due to the influence of downward motion of the mitral plane in the diastolic phase of LA.[30-32] LV hypertrophy (LVH) may also contribute to LA dysfunction through pressure overload and increased LA wall tension; and worse LA strain has been shown to differentiate pathological LVH from physiologic LVH. [33,34] Thus, worse LV systolic function, greater LV hypertrophy and increased LA volume may play a pathophysiologic role in LA dysfunction associated with HFpEF. Higher LV filling pressures may lead to deterioration of LA function as a result of hemodynamic overload and mechanical stretch of the LA wall.[35,36] We did not find an independent association between E/E' or NT-proBNP with LA strain in our HFpEF group, which may be secondary to the fact that all patients enrolled in PARAMOUNT were required to have an elevated NT-proBNP.

Several limitations of our analysis should be noted. We analyzed a subset of the patients enrolled in the PARAMOUNT trial due to technical and quality requirements for

LA speckle tracking analysis and high prevalence of AF at time of echocardiography, with some notable differences between the included and excluded patients. Although the analyses of three-dimensional images may be a more accurate measurement, the protocol of PARAMOUNT trial required only two-dimensional images.[37] In addition, the generalizability of these findings to HFpEF patients in the community may be limited because of the inclusion/exclusion criteria of the overall PARAMOUNT trial.

In summary, LA dysfunction was present among HFpEF patients and impaired LA reservoir function occurred regardless of LA size or history of AF. In HFpEF patients, lower systolic LA strain was associated with higher prevalence of prior heart failure hospitalization and history of AF, as well as worse LV systolic function, LV hypertrophy and LA remodeling, suggesting that LA dysfunction may be a marker of severity in HFpEF and may further play a pathophysiologic role in HFpEF. The additional clinical and prognostic relevance of LA function in HFpEF remains to be determined.

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Conflict of interest: Drs. MRZ, BP, AAV, MP, JJVM, AMS and SDS have received research support and have consulted for Novartis. Drs. ML, TB and VS are employees of Novartis. Drs. ABSS, EKK, DKG and BC declare that they have no conflict of interest.

References

1 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–259.

2 Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;**355**:260–269.

3 Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012;**33**:1750-1757.

4 Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal Relationship and Prognostic Significance of Atrial Fibrillation in Heart Failure Patients with Preserved Ejection Fraction: A Community-Based Study. *Circulation* 2013;**128**:1085-1093.

5 Tsutsui H, Tsuchihashi M, Takeshita A. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. *Am J Cardiol* 2001;**88**:530-533.

6 Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007;**50**:768-777.

7 Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;**350**:1953-1959.

8 Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011;**32**:670-679.

9 Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol* 2005;**45**:87-92.

10 Tsang TS, Barned ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol* 2002;**90**:1284-1289.

11 Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, Baicu CF, Massie BM, Carson PE; I-PRESERVE Investigators. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation* 2011;**124**:2491-501.

12 Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ, Ostergren J, McKelvie RS; Investigators of the CHARM Echocardiographic Substudy-CHARMES. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy–CHARMES. *J Am Coll Cardiol* 2007;**49**:687– 694.

13 Morris DA, Gailani M, Vaz Pérez A, Blaschke F, Dietz R, Haverkamp W, Ozcelik C.. Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. *J Am Soc Echocardiogr* 2011;**24**:651-662.

14 Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, Lakatta EG, Najjar SS, Kass DA.. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. *J Am Coll Cardiol* 2007;**49**:198-207.

15 Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators.. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;**380**:1387–1395.

16 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography.
. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440-63.

17 Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation

of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;**10**:165-93.

18 Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, Marino E, Galderisi M. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. *Cardiovasc Ultrasound* 2009;**8**;7:6.

19 Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography--from technical considerations to clinical applications. *J Am Soc Echocardiogr* 2007;**20**:234-243.

20 Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD; PARAMOUNT Investigators.Impaired Systolic Function by Strain Imaging in Heart Failure with Preserved Ejection Fraction. J Am Coll Cardiol. 2014;**63**:447-56.

21 Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons > or =65 years of age (the cardiovascular health study). *Am J Cardiol*. 2006;**97**:83-89.

22 Tan YT, Wenzelburger F, Lee E, Nightingale P, Heatlie G, Leyva F, Sanderson JE. Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction. *Heart* 2010;**96**:1017-1023.

23 Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. *Circ Cardiovasc Imaging* 2009;**2**:10-15.

24 Boyd AC, Richards DA, Marwick T, Thomas L. Atrial strain rate is a sensitive measure of alterations in atrial phasic function in healthy ageing. *Heart* 2011;**97**:1513-1519.

25 Zhang Q, Yip GW, Yu CM. Approaching regional left atrial function by tissue Doppler velocity and strain imaging. *Europace* 2008;**10**:62-69.

26 Motoki H, Borowski AG, Shrestha K, Troughton RW, Martin MG, Tang WH, Klein AL. Impact of Left Ventricular Diastolic Function on Left Atrial Mechanics in Systolic Heart Failure. *Am J Cardiol* 2013;**112**:821-826.

27 Welles CC, Ku IA, Kwan DM, Whooley MA, Schiller NB, Turakhia MP. Left atrial function predicts heart failure hospitalization in subjects with preserved ejection fraction and coronary heart disease: longitudinal data from the Heart and Soul Study. *J Am Coll Cardiol* 2012;**59**:673-680.

28 Kojima T, Kawasaki M, Tanaka R, Ono K, Hirose T, Iwama M, Watanabe T, Noda T, Watanabe S, Takemura G, Minatoguchi S.. Left atrial global and regional function in patients with paroxysmal atrial fibrillation has already been impaired before enlargement of left atrium: velocity vector imaging echocardiography study. *Eur Heart J Cardiovasc Imaging* 2012;**13**:227–234.

29 Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, Rao SN, Blauer J, Fish EN, Dibella EV, Macleod RS, McGann C, Litwin SE, Marrouche NF. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. *Circ Cardiovasc Imaging* 2010;**3**:231-9.

30 Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation* 1999;**100**:427-436.

31 Ersbøll M1, Andersen MJ, Valeur N, Mogensen UM, Waziri H, Møller JE, Hassager C, Søgaard P, Køber L.The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. *Circ Cardiovasc Imaging* 2013;**6**:26-33.

32 Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR.. Left atrial minimum volume and reservoir function as correlates of left ventricular diastolic function: impact of left ventricular systolic function. *Heart* 2012;**98**:813-820.

33 D'Andrea A, De Corato G, Scarafile R, Romano S, Reigler L, Mita C, Allocca F, Limongelli G, Gigantino G, Liccardo B, Cuomo S, Tagliamonte G, Caso P, Calbrò R. Left atrial myocardial function in either physiological or pathological left ventricular hypertrophy: a two-dimensional speckle strain study. *Br J Sports Med* 2008;**42**:696-702.

34 Gabrielli L, Enríquez A, Córdova S, Yáñez F, Godoy I, Corbalán R. Assessment of left atrial function in hypertrophic cardiomyopathy and athlete's heart: a left atrial myocardial deformation study. *Echocardiography* 2012;**29**:943-949.

35 Guan Z, Zhang D, Huang R, Zhang F, Wang Q, Guo S. Association of left atrial myocardial function with left ventricular diastolic dysfunction in subjects with preserved systolic function: a strain rate imaging study. *Clin Cardiol* 2010;**33**:643-649.

36 Prioli A, Marino P, Lanzoni L, Zardini P. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. *Am J Cardiol* 1998;**82**:756-61**.**

37 Nagaya M, Kawasaki M, Tanaka R, Onishi N, Sato N, Ono K, Watanabe T, Minatoguchi S, Miwa H, Goto Y, Hirose T, Arai M, Noda T, Watanabe S, Minatoguchi S. Quantitative validation of left atrial structure and function by two-dimensional and three-dimensional speckle tracking echocardiography: a comparative study with three-dimensional computed tomography. *J Cardiol* 2013 **62**:188-94.

Figure legends

Figure 1: Two-dimensional speckle tracking imaging in the apical four-chamber view in a healthy patient.

Legend: Left panel presents left atrial (LA) phasic volumes (orange curve); middle panel presents LA reservoir function measured by strain, and right panel presents LA conduit function (first negative peak) and LA pump function (second negative peak) assessed by strain rate.

Figure 2: Comparison of left atrial function (reservoir, conduit and pump function) between healthy controls (gray bar) and HFpEF patients (black bar).

Legend: Data are shown as mean ± SE

LA= left atrial.

*p value adjusted for age, gender, heart rate, systolic blood pressure, body mass index, LA volume index, LV global longitudinal strain and E/E'.

Figure 3: Comparison of left atrial (LA) reservoir function (measured by systolic LA strain) among healthy controls, and HFpEF patients with normal LA volume ($\leq$29ml/m^2) and with LA enlargement (>29ml/m^2).

Legend: Data are shown as mean ± SE.

*unadjusted p value (<0.01).

†p value (< 0.01) adjusted for age, gender, heart rate, systolic blood pressure, body mass index, LV global longitudinal strain and E/E'.

Figue 4: Comparison of LA reservoir function (measured by systolic LA strain) among healthy controls, and HFpEF patients without and with known history of atrial fibrillation (AF).

Legend: Data are shown as mean ± SE.

*unadjusted p value (<0.001).

†p value (< 0.01) adjusted for age, gender, heart rate, systolic blood pressure, body mass index, LV global longitudinal strain and E/E'.

Table 1: Baseline characteristics of the study population

	Controls (n=40)	**HFpEF (n=135)**	**p value**
Age (years)	68 ± 6	70 ± 9	0.051
Women, n (%)	27 (68)	83 (61)	0.49
NYHA II, n (%)	--	108 (81)	
NYHA III, n (%)	--	26 (19)	
Previous Hospitalization for HF, n (%)	0 (0)	66 (50)	
History of Atrial Fibrillation, n (%)	0 (0)	31 (23)	
History of Hypertension, n (%)	0 (0)	123 (92)	
History of Diabetes, n (%)	0 (0)	47 (35)	
History of Myocardial Infarction, n (%)	0 (0)	30 (22)	
Heart Rate (beats per min)	71 ± 14	66 ± 13	0.04
Systolic Blood Pressure (mm Hg)	127 ± 15	139 ± 16	<0.001
Diastolic Blood Pressure (mm Hg)	74 ± 11	78 ± 11	0.04
Body Mass Index (kg/m^2)	25.2 ± 3.7	29.6 ± 5.7	<0.001
NT-proBNP (pg/mL)	--	809 [446,1300]	
Baseline treatments			
ACE inhibitors or ARBs, n (%)	0(0)	125(93)	
Diuretic, n (%)	0(0)	135 (100)	
B Blockers, n (%)	0(0)	109(81)	
Aldosterone Antagonists, n (%)	0(0)	24(18)	

Echocardiographic measures			
LV Ejection Fraction (%)	60 ± 3	59 ± 7	0.22
Global Longitudinal Strain (%)	-19.9 ± 2.2	-15.0 ± 3.4	<0.001
LV End-Diastolic Volume (mL)	85.2 ± 24.5	114.1 ± 28.1	<0.001
LV End-Diastolic Volume /BSA (mL/m^2)	48.4 ± 11.0	61.8 ± 14.3	<0.001
LV End-Systolic Volume (mL)	34.9 ± 13.6	47.3 ± 16.4	<0.001
LV End-Systolic Volume/BSA (mL/m^2)	19.6 ± 6.5	25.5 ± 8.5	<0.001
Relative Wall Thickness	0.42 ± 0.07	0.38 ± 0.09	0.004
LV Mass Index (g/m^2)	77.5 ± 17.0	79.4 ± 21.8	0.57
LV Mass/height$^{2.7}$ (g/$m^{2.7}$)	35.7 ± 7.6	38.5 ± 11.3	0.09
E' (cm/s)	9.4 ± 2.1	6.6 ± 2.4	<0.001
A' (cm/s)	10.8 ± 2.8	7.2 ± 2.5	<0.001
E/E'	7.5 ± 2.5	13.7 ± 8.6	<0.001
A wave (cm/s)	72.2 ± 18.0	74.0 ± 27.6	0.63
E/A	0.95 ± 0.23	1.20± 0.67	<0.001
Left Atrial Volume Index (mL/m^2)	21.1 ± 5.3	33.4 ± 11.5	<0.001

Data are presented as n (%) and mean ± SD.

p values was calculated by *ttest* or X^2

NYHA= New York Heart Association. ACE= angiotensin-converting enzyme.

ARB=angiotensin receptor blocker. E'= early lateral mitral relaxation velocity. A'= late lateral mitral relaxation velocity. E/E'=mitral inflow to mitral relaxation velocity ratio.

E/A=early to late mitral inflow velocity ratio. A= late mitral inflow velocity ratio. LA= Left Atrial.

Table 2: Characteristics of patients with HFpEF by quartiles of systolic **LA strain**

	Quartiles of systolic **LA strain**				
	Worse			**Better**	
	15.7 ± 2.9 (n=34)	**22.2 ± 1.3 (n=34)**	**26.9 ± 1.5 (n=34)**	**34.1 ± 4.3 (n=33)**	**p-for trend**
Age (years)	70 ± 9	72 ± 8	72 ± 11	67 ± 8	0.18
Female, n (%)	19(56)	27(79)	18(53)	19(58)	0.57
BMI (kg/m^2)	30.0 ± 5.3	29.5 ± 6.5	29.6 ± 5.6	29.3 ± 5.4	0.67
HR (beats per min)	63 ± 9	67 ± 12	67 ± 18	67 ± 13	0.17
SBP (mm Hg)	141 ± 17	139 ± 15	135 ± 19	140 ± 13	0.66
Previous HF Hosp, n (%)	23(68)	19(56)	16(47)	8(26)	0.001
History of AF, n (%)	15(45)	5(15)	7(21)	4(12)	0.004
History of HTN, n (%)	29(88)	32(94)	31(91)	31(94)	0.48
History of DM, n (%)	11(33)	11(32)	13(38)	12(36)	0.68
History of MI, n (%)	9(27)	3(9)	10(29)	8(24)	0.71
LVEF (%)	56.5 ± 6.2	59.8 ± 7.6	58.8 ± 8.3	61.2 ± 6.2	0.02
LV GLS (%)	-13.5 ± 3.0	-14.7 ± 3.6	-15.3 ± 3.1	-16.7 ± 3.1	<0.001
RWT	0.37 ± 0.11	0.38 ± 0.08	0.39 ± 0.08	0.38 ± 0.08	0.55
LV Mass Index (g/m^2)	84.5 ± 27.8	78.3 ± 19.4	80.7 ± 16.7	74.1 ± 21.1	0.09
LV Mass/$height^{2.7}$ ($g/m^{2.7}$)	41.9± 15.2	37.9 ± 9.4	38.8 ± 8.0	35.2 ± 10.6	0.03
LAVi (mL/m^2)	40.3 ± 14.3	32.8 ± 9.0	32.7 ± 9.8	27.5 ± 8.5	<0.001
E’ (cm/s)	6.7 ± 3.0	6.3 ± 1.7	6.9 ± 2.6	6.3 ± 2.0	0.82

E/E' (cm/s)	15.6 ± 14.3	14.0 ± 6.5	12.5 ± 5.5	12.7 ± 4.8	0.14
NT-proBNP(pg/ml)	948 [601-1914]	727 [499-1697]	620 [399-1004]	830 [374-1198]	0.07

Data are shown as mean ± SD, median [IQR] or n (percentage).

BMI = Body Mass Index; HR=Heart Rate; SBP= Systolic Blood Pressure; LV= left ventricular; LAVi= left atrial volume index; LVEF= left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain; RWT= Relative Wall Thickness; E'= early lateral mitral relaxation velocity

Figure 1

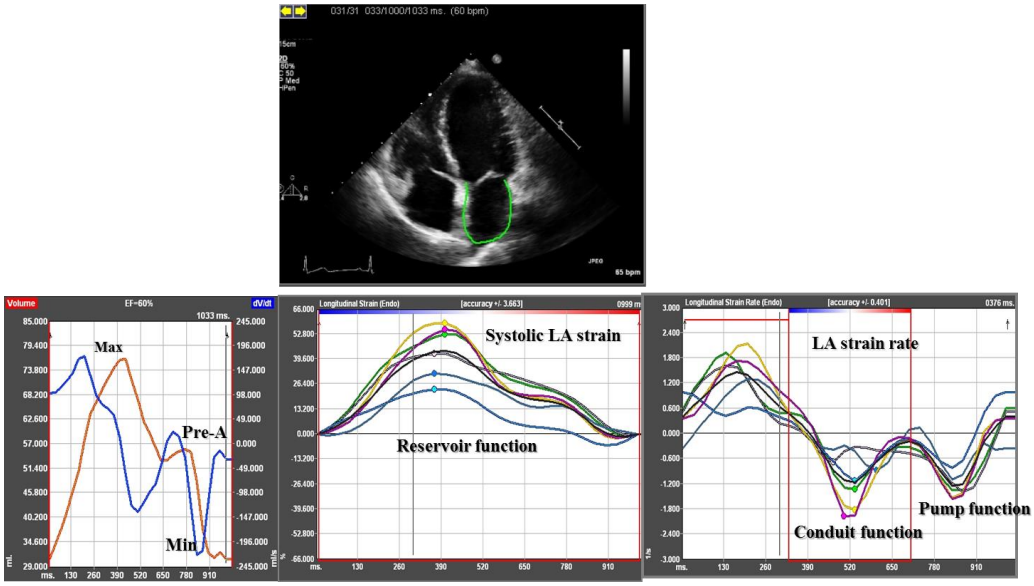

Max
Pre-A
Min
Systolic LA strain
Reservoir function
LA strain rate
Conduit function
Pump function

Figure 2

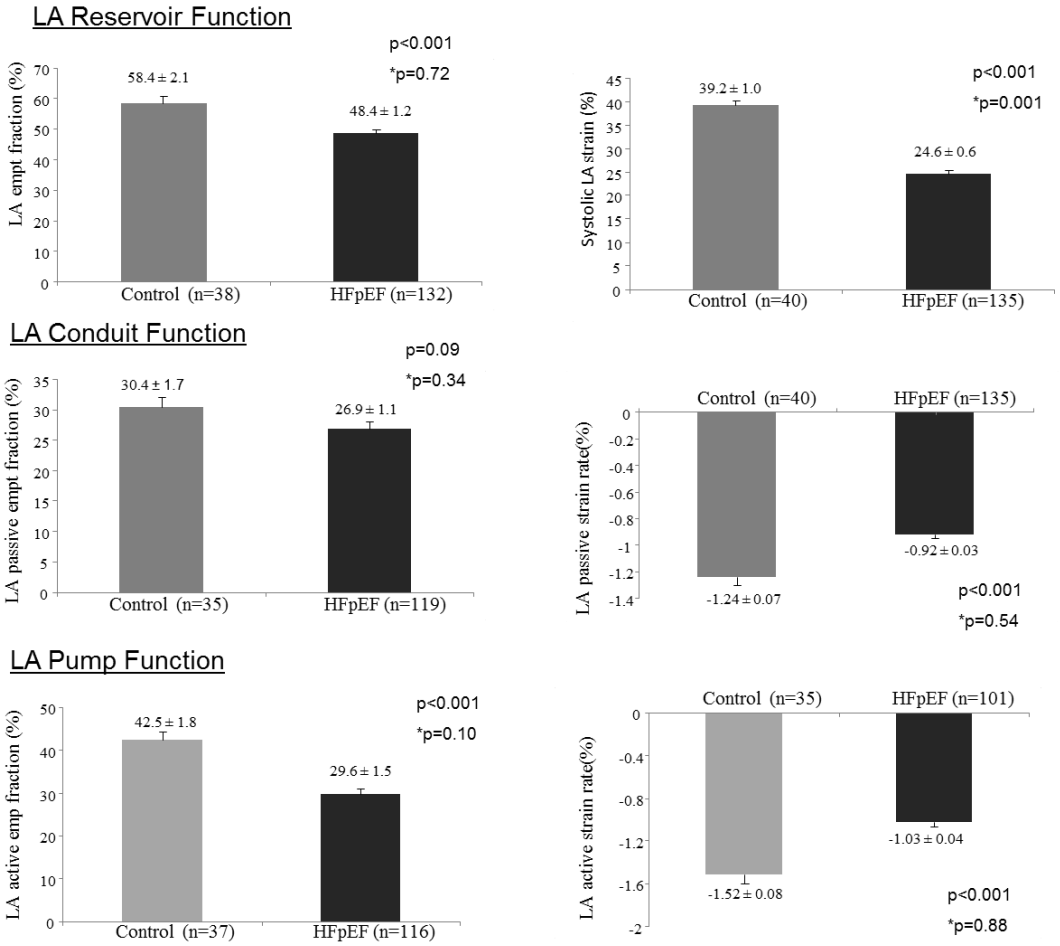

LA Reservoir Function
p<0.001
*p=0.72
LA empt fraction (%)
58.4 ± 2.1
48.4 ± 1.2
Control (n=38)
HFpEF (n=132)
Systolic LA strain (%)
39.2 ± 1.0
24.6 ± 0.6
p<0.001
*p=0.001
Control (n=40)
HFpEF (n=135)
LA Conduit Function
p=0.09
*p=0.34
LA passive empt fraction (%)
30.4 ± 1.7
26.9 ± 1.1
Control (n=35)
HFpEF (n=119)
LA passive strain rate(%)
-1.24 ± 0.07
-0.92 ± 0.03
p<0.001
*p=0.54
LA Pump Function
p<0.001
*p=0.10
LA active emp fraction (%)
42.5 ± 1.8
29.6 ± 1.5
Control (n=37)
HFpEF (n=116)
LA active strain rate(%)
-1.52 ± 0.08
-1.03 ± 0.04
Control (n=35)
HFpEF (n=101)
p<0.001
*p=0.88

Figure 3

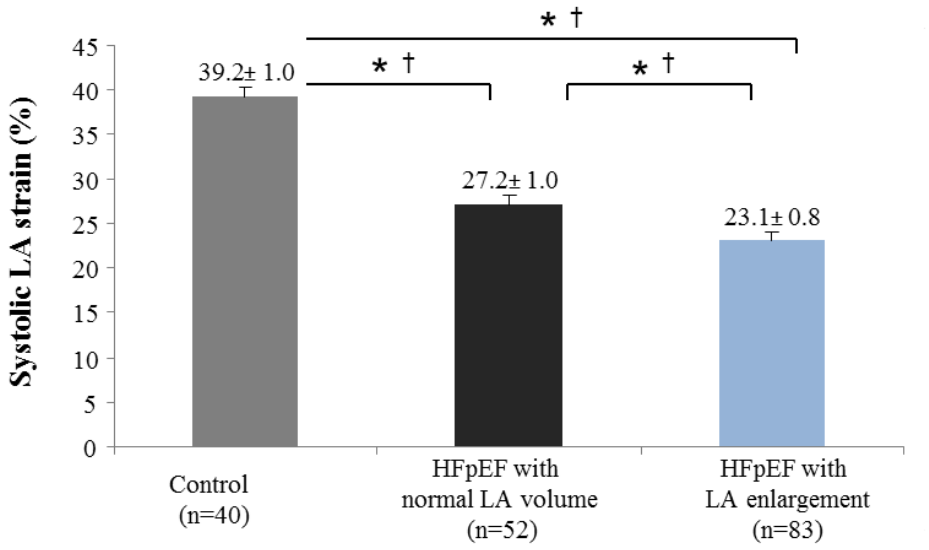
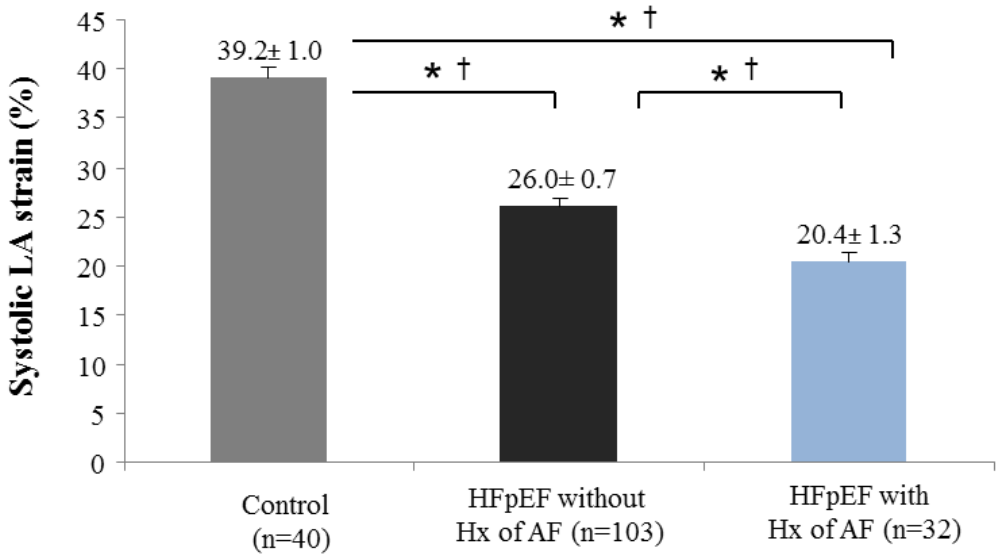

* †
* †
* †
39.2± 1.0
27.2± 1.0
23.1± 0.8
Systolic LA strain (%)
45
40
35
30
25
20
15
10
5
0
Control
(n=40)
HFpEF with
normal LA volume
(n=52)
HFpEF with
LA enlargement
(n=83)

Figure 4


Systolic LA strain (%)
45
40
35
30
25
20
15
10
5
0
39.2± 1.0
26.0± 0.7
20.4± 1.3
* †
* †
* †
Control (n=40)
HFpEF without Hx of AF (n=103)
HFpEF with Hx of AF (n=32)

Conclusões

Nessa amostra relativamente grande e bem caracterizada de pacientes com Insuficiência Cardíaca com Fração de Ejeção Preservada, nós encontramos maior dissincronia mecânica do ventrículo esquerdo, prejuízo na função sistólica do ventrículo esquerdo quando avaliada pelo *strain* na sua deformação longitudinal e circunferencial e disfunção do átrio esquerdo. Esse mecanismos podem ter um papel na complexa e heterogênea fisiopatologia da ICFEP. A relevância clínica e prognóstica de todos esses achados ainda estão por ser determinadas.