Abnormal Coronary Flow Velocity Reserve and Decreased Myocardial Contractile Reserve Are Main Factors in Relation to Physical Exercise Capacity in Cardiac Amyloidosis

Tor Skibsted Clemmensen, MD, PhD, Hans Eiskjær, MD, DMSc, Henning Mølgaard, MD, DMSc, Anders Hostrup Larsen, MD, Jens Soerensen, MD, DMSc, Niels Frost Andersen, MD, PhD, Lars Poulsen Tolbod, PhD, Hendrik J. Harms, PhD, and Steen Hvitfeldt Poulsen, MD, DMSc, *Skejby, Denmark*

Background: The aim of the present study was to evaluate the clinical importance of echocardiographic coronary flow velocity reserve (CFVR), resting and exercise left ventricular global longitudinal strain (LVGLS), and myocardial work efficiency (MWE) in patients with cardiac amyloidosis (CA).

Methods: The study population comprised 69 subjects: group A, 27 patients with CA confirmed by endomyocardial biopsy (CA positive); group B, 42 healthy control subjects. The amyloid phenotype in group A was as follows: patients with wild-type transthyretin-related amyloidosis ($n = 10$), carriers of the Danish familial transthyretin amyloidosis mutation with cardiac involvement ($n = 5$), and patients with amyloid light chain amyloidosis with cardiac involvement ($n = 12$). All subjects underwent comprehensive echocardiographic evaluation during rest and during symptom-limited, semisupine exercise testing. Furthermore, CFVR was assessed using Doppler echocardiography.

Results: Patients with CA had significantly lower CFVR (1.7 ± 0.6 vs 3.9 ± 0.8, $P < .0001$), MWE (1.9 ± 1.0 vs 3.0 ± 0.7, $P < .0001$), and LVGLS magnitude (11% [10%–14%] vs 20% [18%–21%], $P < .0001$) than control subjects. Patients with CA showed severely reduced deformation and efficiency reserve compared with control subjects (ΔLVGLS 0.9 ± 2.8% vs 5.6 ± 2.3%, $P < .0001$; ΔMWE 2.5 ± 2.8 vs 8.8 ± 2.6, $P < .0001$). In patients with CA, a strong relation was seen between physical capacity by the metabolic equivalent of tasks test and CFVR ($r = 0.55$, $P < .01$), peak exercise LVGLS ($r = 0.64$, $P < .0001$), and peak exercise MWE ($r = 0.60$, $P < .01$).

Conclusions: Patients with CA had a profound lack of CFVR and longitudinal myocardial deformation reserve compared with healthy control subjects. Both parameters were significantly associated with exercise capacity and may prove useful for evaluating cardiac performance in patients with CA. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Cardiac amyloidosis, Positron emission tomography, Coronary flow velocity reserve, Heart failure, Speckle-tracking

Cardiac amyloidosis (CA) is characterized by extracellular deposition of misfolded proteins, leading to increased biventricular wall thickness and myocardial stiffness.[1-3] Furthermore, amyloid deposits are frequently seen in relation to intramural coronary arteries.[4-6] Amyloid deposits often cause restrictive heart failure. In some cases, the presence of obstructive intramural coronary amyloidosis may lead to ischemic heart failure.[6] Because of these deposits, patients with CA have severely reduced exercise capacity.[7] Echocardiography remains the most widely used modality with which to characterize myocardial function in relation to these deposits. Previous studies of resting left ventricular global longitudinal strain (LVGLS) demonstrated great clinical value of this modality. Hence, this long-axis functional parameter has both diagnostic and prognostic value in patients with cardiac amyloid deposits.[8-16] The longitudinal muscle fibers of the left ventricle are located predominantly in the endocardium, which makes long-axis function very sensitive to perfusion abnormalities. Coronary flow reserve represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands. A single small study evaluated coronary flow reserve in patients with CA using ^{13}N ammonia positron emission tomography (PET). The results revealed

From the Department of Cardiology (T.S.C., H.E., H.M., A.H.L., S.H.P.), the Department of Nuclear Medicine & PET Center (J.S., L.P.T., H.J.H.), and the Department of Hematology (N.F.A.), Aarhus University Hospital, Skejby, Denmark.

Conflicts of Interest: none.

Funding was received from the Health Research Fund of the Central Denmark Region and from the Danish Heart Association.

Reprint requests: Tor Skibsted Clemmensen, MD, Aarhus University Hospital Skejby, Department of Cardiology, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark (E-mail: *torclemm@rm.dk*).

0894-7317/$36.00

https://doi.org/10.1016/j.echo.2017.09.007

Abbreviations

2D = Two-dimensional

3D = Three-dimensional

AL = Amyloid light chain

ATTRm = Familial transthyretin-related amyloidosis

CA = Cardiac amyloidosis

CFVR = Coronary flow velocity reserve

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVGLS = Left ventricular global longitudinal strain

LVOT = Left ventricular outflow tract

METs = Metabolic equivalent of tasks

MWE = Myocardial work efficiency

PET = Positron emission tomography

PIB = Pittsburgh compound B

RPP = Rate pressure product

RV = Right ventricular

a profoundly reduced myocardial perfusion reserve in patients with CA, indicating microvascular dysfunction.[17] However, the link between microvascular perfusion, myocardial contractile reserve, and exercise capacity in patients with CA has not been studied. Hence, in the present study we aimed to evaluate cardiac performance in terms of myocardial work efficiency (MWE), LVGLS during exercise stress, and coronary flow velocity reserve (CFVR) in patients with CA. Furthermore, we aimed to determine the relation among exercise capacity, CFVR, and contractility.

METHODS

Patients

We prospectively enrolled 27 patients with CA (group A) and 42 healthy control subjects (group B) in the Department of Cardiology, Aarhus University Hospital, from January 2014 to November 2016. In this period, we invited all patients with CA followed or referred to our center to participate in the study. Four patients declined participation. Group A consisted of patients with wild-type transthyretin-related amyloidosis ($n = 10$), familial transthyretin-related amyloidosis (ATTRm) mutation carriers with cardiac involvement ($n = 5$), and patients with amyloid light chain (AL) amyloidosis with cardiac involvement ($n = 12$).

Four patients (three with AL amyloidosis, one with ATTRm) had positive results on ^{11}C–Pittsburgh compound B PET[18,19] but were not subjected to endomyocardial biopsy. These patients were grouped as CA positive (group A), even though we could not rule out false-positive results on ^{11}C–Pittsburgh compound B PET.

All individuals were ≥18 years of age and were included after having provided written informed consent in pursuance of the principles of the Declaration of Helsinki. The healthy control subjects and healthy mutation carriers received no medications, had no cardiopulmonary symptoms, and had normal findings on electrocardiography. The patients were included from our outpatient clinic. We excluded patients with significant valve disease or significant chronic obstructive pulmonary disorder. The local Scientific Ethics Committee of the Central Denmark Region approved the study.

Echocardiography

We used a commercially available ultrasound system (Vivid 9E; GE Vingmed Ultrasound, Horten, Norway) with a 3.5-MHz phased-array transducer (M5S).

At rest, patients underwent comprehensive echocardiographic assessment according to current guidelines.[20] At each stage of exercise, we assessed two-dimensional (2D) cine loops and tissue Doppler images from all three apical views of the left ventricle along with pulsed-wave Doppler of the mitral inflow and the left ventricular outflow tract (LVOT). Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method of disks. Peak systolic mitral annular velocity (S′) was estimated from the tissue Doppler velocity images as the average of septal, lateral, anterior, and posterior velocities. The magnitude of LVGLS[21] was obtained from frame-by-frame tracking of speckle patterns throughout the left-sided myocardium in standard 2D cine loops with a frame rate > 55 frames/sec. The speckle area of interest was adjusted manually to achieve optimal tracking results. Segments with unacceptably low tracking quality were excluded. LVGLS was calculated at the time in systole when the value peaked, using a 17–myocardial segment model.[22] In this article, strain and changes in strain are reported in absolute terms.

We obtained three-dimensional (3D) left ventricular (LV) mass by sampling six heartbeats during breath-hold, aiming at a frame rate > 25 frames/sec using a 4V-D transducer. We measured both diastolic and systolic LV mass. An average of the two measurements indexed to body surface area was used as marker of amyloid burden. LV mass by 3D echocardiography has been validated in several studies showing that LV mass measured by 3D echocardiography is similar to that measured by magnetic resonance imaging.[23-26]

Free-wall right ventricular (RV) global longitudinal strain was assessed from a modified four-chamber view averaging the three lateral segments. Tricuspid annular systolic velocity wave (RV S′) was assessed from lateral, pulsed tissue Doppler velocities. Likewise, tricuspid annular plane systolic excursion was measured from the lateral tricuspid plane. Three-dimensional RV ejection fraction was obtained by sampling six heartbeats during breath-hold from a modified four-chamber view aiming at a frame rate > 25 frames/sec.

We calculated the work-pressure product as LVOT area × velocity-time integral × heart rate × mean arterial blood pressure. MWE was calculated as work pressure product/3D LV mass.

For the interobserver reproducibility analysis, two observers analyzed 20 randomly selected stress echocardiograms. The same echocardiograms were used in the intraobserver repeatability analyses. The two observers were blinded to each other's analysis. We calculated the intraclass correlation coefficient and the coefficient of variation.

Data were analyzed offline using dedicated software (EchoPAC PC SW-Only version 201 [GE Healthcare, Milwaukee, WI] and TomTec 4D RV-Function [TomTec Imaging Systems, Munich, Germany]).

Assessment of CFVR

CFVR was assessed on echocardiography in a modified apical view of the distal part of the left anterior descending coronary artery using a high-frequency broadband transducer (S6-D; GE Healthcare). All subjects abstained from consuming caffeine-containing drinks for 24 hours before testing. Coronary flow velocity was obtained using color Doppler flow mapping guidance. Subsequently, a sample volume was positioned on the color signal in the artery using pulsed-wave Doppler. After baseline recording, intravenous adenosine infusion (140 μg/kg/min) was administered for ≥120 sec. Hyperemic flow profiles were recorded in the same angle and position as the resting recordings. In case of low increase in the flow velocity within 120 sec of adenosine challenge, infusion was continued for up to 300 sec. At least two well-defined cycles were obtained at rest