Echocardiographic Abnormalities in Adults With Anorexia Nervosa

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Anorexia nervosa (AN) is a psychiatric disorder that may lead to cardiac complications. The objective of this study was to evaluate global and regional longitudinal strain changes in patients affected by AN as an early marker of myocardial damage. We prospectively enrolled 48 consecutive patients with AN and 44 age-matched and gender-matched healthy controls. In all subjects, we performed echocardiography, including global longitudinal strain (GLS) measurement. A subset of 33 patients with AN had further echocardiographic examinations during the follow-up. Compared with healthy controls, patients with AN had a greater prevalence of pericardial effusion (9 of 48 vs 0 of 44, p = 0.003), a smaller left ventricular mass (63 ± 15 vs 99 ± 30 g, p < 0.001), a lower absolute value of GLS (−18.9 ± 2.8 vs −20.2 ± 1.8%, p = 0.010) and of basal LS (−15.4 ± 6.0 vs −19.4 ± 2.6%, p < 0.001). The bull's eye mapping showed a plot pattern with blue basal areas in 18 of 48 patients with AN versus 1 of 44 controls (p < 0.001). During the follow-up, of 13 patients with blue areas in the first bull's eye mapping, 11 recovered completely, and of 20 patients with a red bull's eye at the first examination, none presented blue areas at the second one. In conclusion, GLS is significantly altered in patients with AN, and a basal blue pattern on bull's eye mapping identifies more severe cases. These changes seem to be reversible. **(Am J Cardiol 2022;175:152−157)**

Anorexia nervosa (AN) is a psychiatric disorder with potential cardiac complications, especially in severely malnourished patients. Cardiovascular involvement includes autonomic dysfunction (increased vagal tone, bradycardia, orthostatic hypotension, syncope), arrhythmias, pericardial effusion, heart failure, and sudden death.[1] A few studies of the echocardiographic abnormalities secondary to AN have reported mainly a decreased left ventricular mass and an increased incidence of pericardial effusion.[2,3] In contrast, data on changes of global longitudinal strain (GLS),[4,5] which has been shown to be an early marker of myocardial damage in other clinical subsets,[6] are substantially limited. This study aimed to assess whether, in the echocardiographic abnormalities potentially associated with AN, either GLS or segmental LS are impaired and of possible clinical significance in this psychiatric disorder.

Methods

We prospectively enrolled 48 consecutive patients admitted to a highly specialized psychiatric unit between November 2020 and July 2021 with a diagnosis of AN that had been suspected following the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition,[7] and was then confirmed by a formal psychiatric evaluation. We also enrolled 44 age-matched and gender-matched volunteers as healthy controls. Co-morbidities excluded enrollment. The study was approved by the local Ethics Committee in keeping with statements by the Italian Regulatory Authorities for observational studies (*https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552*), granted a waiver of informed consent from study participants. Data for analysis were obtained from electronic hospital charts, anonymized, and protected by a password. Body mass index (BMI, kg/m^2), heart rate, systolic and diastolic blood pressure, routine blood tests, an electrocardiogram, and an echocardiography examination that included 2D speckle tracking measurement were recorded in all cases. We used a General Electric VIVID E9 (General Electric, Fairfield, Connecticut) device. Images were analyzed using the EchoPAC Software package (GE Healthcare) with a 17 segments model. In the analysis of ventricular GLS, a conventional color-coding map is used in which normally contracting segments are depicted as red, whereas those with reduced contractility are represented as blue segments. In healthy patients, the average peak GLS ranges from −18% to −20%. BMI was normalized for the expected value for age (50th percentile of World Health Organization charts).[8] A single, experienced physician acquired echocardiographic images. Left ventricular mass was calculated with the Devereux formula as $0.8\times1.04\times[(LVDd+IVS+PW)^3-LVDd^3]+0.6$, where

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See page 156 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2022.03.061

Table 1
Clinical characteristics, laboratory examinations, and echocardiographic parameters of patients with and without Anorexia Nervosa

Variable	Anorexia nervosa (n=48)	Healthy controls (n=44)	p Value
Age (years)	23.7±9.2	24.7±3.6	NS
Female	47 (99%)	39 (89%)	NS
Body mass index (kg/m^2)	15.3±1.8	21.1±2.1	<0.001
Active or previous smoker	27 (56%)	4 (9%)	<0.001
Creatinine (mg/dl)	0.7±0.1	0.7±0.1	NS
Albumin (mg/dl)	47.5±11.8	64.8±4.0	0.039
Sodium (mEq/L)	140±3	141±2	NS
Potassium (mEq/L)	4.1±0.5	4.6±0.6	NS
Magnesium (mEq/L)	2.1±0.1	2.0±0.1	NS
Thyroxine stimulating hormone (pg/ml)	1.6±0.9	2.0±1.4	NS
Free triiodothyronine, FT3 (pg/ml)	3.8±1.0	7.9±6.4	<0.001
Free thyroxine, FT4 (pg/ml)	13.9±1.9	9.6±8.1	0.004
Total cholesterol (mg/dl)	163±36	164±21	NS
Low density lipoprotein cholesterol (mg/dl)	87.5±24.7	104.9±20.0	NS
High density lipoprotein cholesterol (mg/dl)	70±15	61±10	NS
Heart rate (beats/min)	61±17	71±12	0.001
Systolic / diastolic arterial pressure (mm Hg)	100±10 / 66±10	109±10 / 72±10	NS
Interventricular septum thickness (mm)	5.7±0.7	7.3±0.9	<0.001
Posterior wall thickness (mm)	5.9±0.7	7.3±0.9	<0.001
Left ventricular end-diastolic diameter (mm)	40±4	44±4	<0.001
Left ventricular end-diastolic volume (ml)	56.2±14.0	74.8±22.0	<0.001
Left ventricular radius : thickness ratio	0.07±0.01	0.08±0.01	<0.001
Left ventricular mass (g)	63±15	99±30	<0.001
Left ventricular ejection fraction (%)	62±4	63±4	NS
Pericardial effusion	9 (19%)	0 (-)	0.003
Tricuspid annular plane excursion (mm)	21±3	24±3	<0.001
Global longitudinal strain (%)	−18.9±2.8	−20.2±1.8	0.010
Mean basal regional strain (%)	−15.4±6.0	−19.4±2.6	<0.001

If not otherwise specified, data are mean ± SD.

LVDd is left ventricular (LV) end-diastolic diameter (mm), whereas IVS and PW are the interventricular septum and posterior wall thickness (mm), respectively. LV systolic function was estimated by calculating the LV ejection fraction (LVEF, %) following the biplane approach. Right ventricular systolic function was estimated by tricuspid annular plane excursion (TAPSE). We calculated the mean LS of basal, median, and apical segments. A total of 18 patients were treated with forced enteral or parenteral feeding as indicated by psychiatric and clinical judgment. All patients underwent nutritional rehabilitation with a nutritionist, and cognitive behavioral therapy with a psychiatrist, with a gradual caloric uptake increase. A subset of 33 patients with AN received 1 or more further echocardiographic examinations during the follow-up at variable time intervals (median time interval between first and last examination: 19 weeks, 95% confidence interval 15 to 22). Overall, 164 clinical evaluations combined with ultrasound examinations were performed. Our primary objective was to compare the clinical and echocardiographic characteristics of patients with and without AN, focusing on GLS. The secondary objective was to assess whether AN-associated echocardiographic abnormalities are reversible with improved nutritional status. The chi-square and Mann-Whitney or Kruskal-Wallis tests were used to compare proportions and continuous variables with normal or non-normal distribution, respectively. Univariable analyses were performed using linear regression and general linear models. Changes of continuous variables over time during the follow-up were analyzed with analysis of variance for repeated measures. Pearson's correlation coefficient was used to analyze the relation between 2 continuous variables, namely BMI and strain. For repeated measures, linear regression with clustered covariances for multiple measures on the same subject has been used. All tests were 2-sided, and statistical significance was defined as a p value <0.05. All analyses were performed with the IBM SPSS Statistics for Windows Version 26 (Armonk, New York) and R Software Version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical, laboratory and echocardiographic data are listed in Table 1. Compared with matched controls, patients with AN were more often active or previous smokers, had lower plasma albumin levels, and lower FT3 associated with higher FT4. They also had a lower heart rate, a greater prevalence of pericardial effusion, a smaller LV mass, and a lower absolute GLS and mean basal LS, whereas LVEF was similar in the 2 groups. Figure 1 shows the distributions of BMI and mean basal longitudinal strain between cases and controls at baseline. At linear regression analysis, BMI correlated directly with LV mass (r = 0.75, p = 0.001), radius: thickness ratio (r = 0.5, p = 0.001), and TAPSE (r = 0.56, p = 0.001); and inversely with GLS (r = 0.3, p = 0.004) and mean basal LS (r = 0.47, p = 0.001). We obtained similar results when BMI was normalized for the

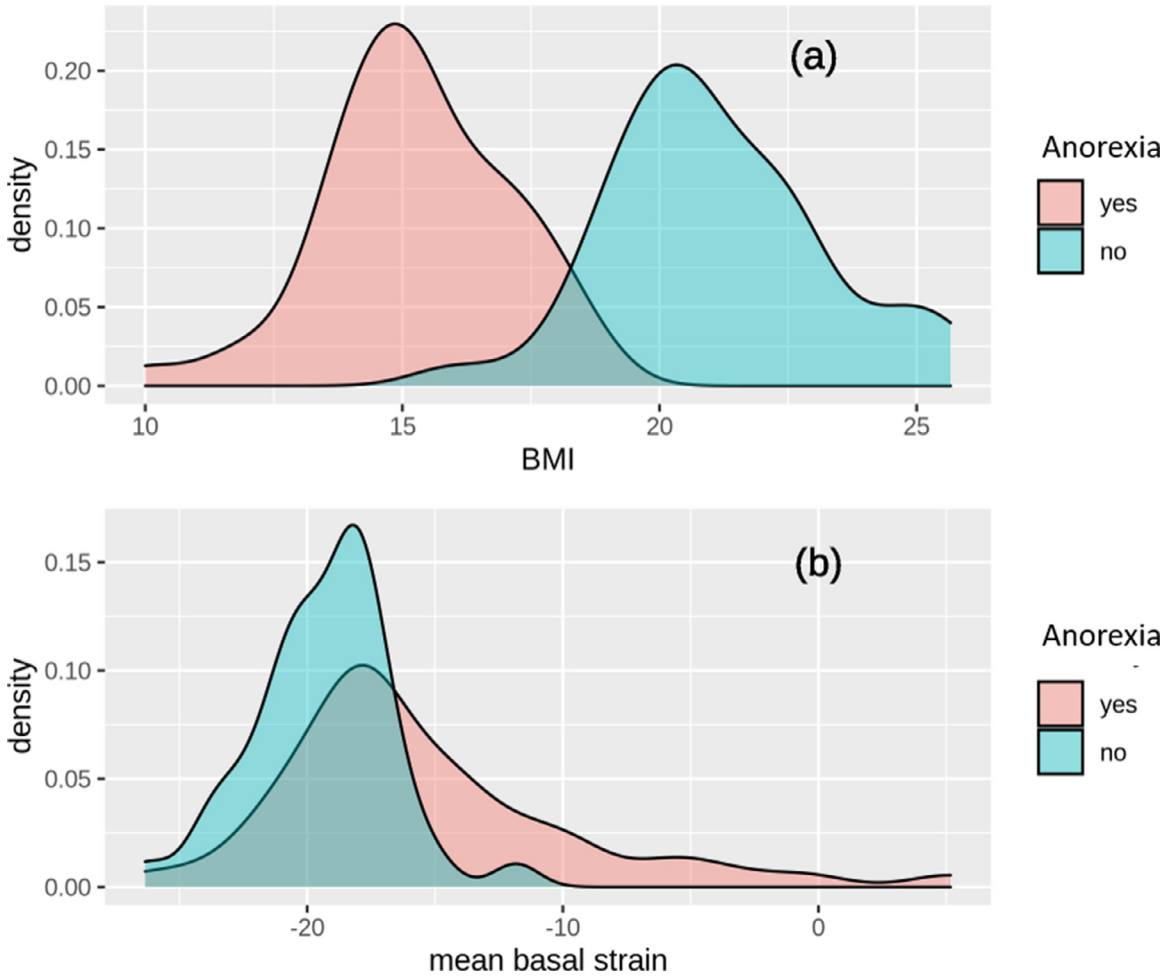

Figure 1. Distribution of BMI *(A)* and mean basal strain *(B)* between anorexic patients and controls.

expected value for age (r = 0.72, p = 0.001; r = 0.49, p = 0.001; r = 0.54, p = 0.001; r = 0.32, p = 0.002; r = 0.52, p = 0.001, respectively). The impairment of GLS did not correlate with thyroid function or heart rate and was not associated with the presence of pericardial effusion or a history of smoking. During bull's eye ventricular color mapping, an abnormal motion pattern, as indicated by blue basal areas, was present in 18 of 48 patients with AN but only in 1 of 44 controls (p <0.001). The 18 patients with AN with GLS-assessed regional ventricular dysfunction required forced feeding in larger proportions than those with a normal motion pattern (12 of 18 vs 8 of 30, p = 0.007). Of 13 patients with blue motion areas at first bull's eye mapping which had a second echocardiographic examination, 11 recovered a completely red (i.e., normal) motion pattern (Figure 2); conversely, none of the 20 patients with a red bull's eye at first examination developed blue areas at the second one.

During the follow-up, there were concomitant improvements in BMI (14.9 ± 1.8 vs 15.9 ± 1.8 kg/m^2, p = 0.001), LV mass (62.0 ± 15.6 vs 68.8 ± 17.4 g/m^2, p = 0.011) and mean basal LS (−14.7 ± 6.3 vs −17.6 ± 3.1%, p = 0.010), whereas GLS, LVEF, and TAPSE did not change significantly (−18.5 ± 2.9 vs −18.2 ± 7.1%; 62.6 ± 3.3 vs 62.4 ± 3.4%; 20.6 ± 2.6 vs 21.4 ± 2.8 mm, respectively). The correlation between BMI and mean basal strain was confirmed repeating linear regression on all (164) evaluations performed, clustering covariances for multiple measures on the same subject (Figure 3).

Discussion

Malnourishment may have systemic consequences, inducing endocrine abnormalities, such as hypogonadotropic hypogonadism, the euthyroid sick syndrome,[9] and cardiovascular abnormalities. In AN, myocardial hypotrophy with LV remodeling has been reported to be the consequence of both decreased afterload and preload and of malnutrition causing atrophy such as that occurring in skeletal muscles. This may worsen biventricular systolic function. As expected, we found a significantly lower longitudinal function of the right ventricle, whereas LV systolic function at rest as assessed by LVEF was normal, as reported in other studies.[10] However, LVEF is influenced by afterload, which in patients with AN is usually reduced along with lower blood pressure. As an early marker of myocardial dysfunction reflecting LV systolic deformation, GLS may reveal myocardial systolic dysfunction earlier

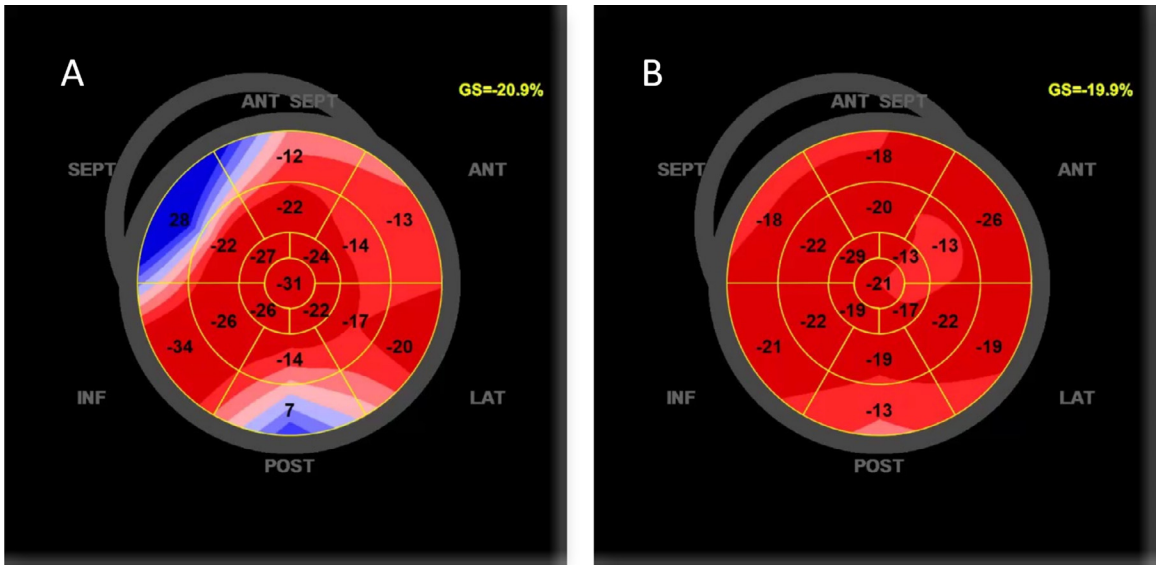

Figure 2. Bull's eye mapping at baseline (*left panel*) and after 2 months of re-nourishing (*right panel*) in the same patient.

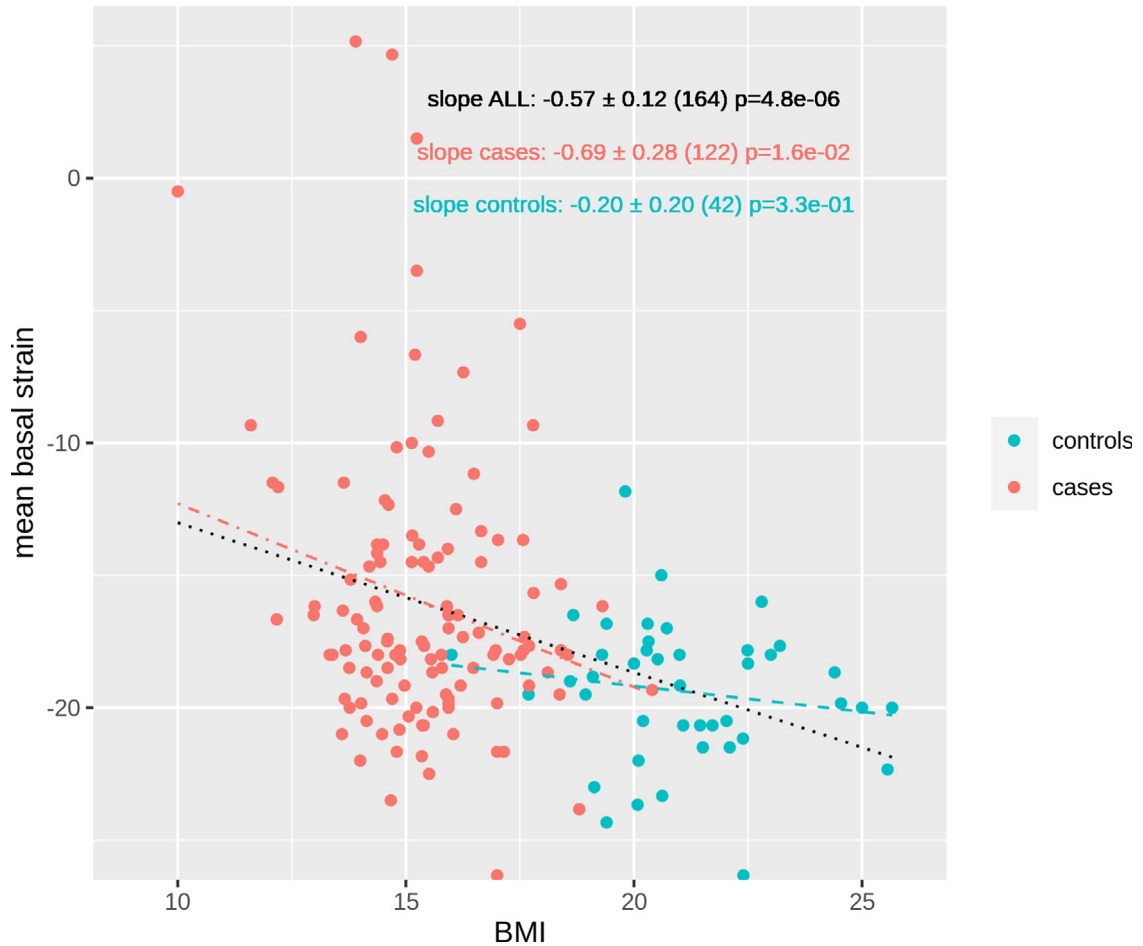

Figure 3. The scatter plot of all (164) evaluations performed, both at baseline and during the follow-up, showing the correlation between BMI and mean basal strain. Each point represents an exam on the plane, where different colors indicate cases and controls. The scatter plot also shows the regression lines obtained by considering all the tests and the cases and controls separately. The regression lines have been adjusted to consider the correlation of repeated tests on the same subjects.

and more sensibly than conventional cavity-based echocardiographic parameters.[11] Automated function imaging based on speckle tracking is a user-friendly advancement to evaluate regional patterns of longitudinal strain.[9] Automated function imaging is usually presented as a bull's eye plot showing color-coded and numerical values for peak systolic LS of all LV segments, providing an intuitive, dynamic overview of systolic function in a single diagram.

The occurrence of myocardial disease can precede the worsening of LVEF and the myocardial structural changes shown by more conventional and usual imaging techniques based on the measurement of LV diameters over the cardiac cycle. Accurate assessment of myocardial function is particularly important in patients at risk of developing a more severe cardiac dysfunction. Geometric factors may determine a reduced regional deformation despite preserved ejection fraction.[12] GLS increases the sensitivity in detecting subclinical cardiac involvement in cardiomyopathies and can be used to evaluate both disease progression and the effects of therapeutic interventions[13] in different clinical settings. Chemotherapy-treated patients with a still normal LVEF may already show an impaired myocardial systolic function as assessed by speckle tracking strain echocardiography.[14] In coronary artery disease, changes in strain facilitate the recognition of ischemic myocardium at rest and during stress echocardiography.[15] Some cardiomyopathies have a typical bull's eye mapping. Regional heterogeneity with basal or mid septal longitudinal strain impairment appears to be distinctive of hypertrophic cardiomyopathy.[16,17] Conversely, a relative apical sparing pattern of LS is typical of amyloidosis.[18] Our results suggest that, in anorexic patients with still preserved global LV function as expressed by LVEF, GLS may detect a myocardial dysfunction with a typical pattern at bull's eye color-coded strain mapping earlier, indicating a worse regional contraction in basal segments. Only 2 other studies have addressed this issue in adolescents (mean age 14 and 16 years) with purging behavior,[4,5] in whom authors found some degree of altered GLS.

The pathophysiology of regional myocardial dysfunction is unclear, but we might hypothesize a pivotal role of the LV apical-basal gradient of β-adrenergic receptors and sympathetic innervation, with the apex characterized by the highest density of β-adrenergic receptors.[19] Therefore, whereas a "catecholamines storm" such as that causing the Tako-Tsubo syndrome would produce maximal tissue damage secondary to adrenergic overstimulation in the apical region, a chronically reduced myocardial contractile function resulting from malnutrition might be less effectively counterbalanced in basal LV regions, provided with less β-adrenergic receptors. Further studies are necessary, including bioelectrical impedance analysis and psychometric variables, to evaluate the relation between the reduction of body muscle mass, anxiety, and myocardial dysfunction.

In our cohort, patients with impaired GLS had more severe AN disease, as suggested by the greater prevalence of amenorrhea and the more frequent indication to force-feed. This reinforces the idea that an accurate echocardiographic screening may identify earlier high-risk patients with potential advantages in their clinical management. Indeed, according to our data obtained in patients with a second echocardiographic examination during the follow-up, the myocardial dysfunction appears to be reversible with improved feeding, as indicated by increased BMI. Our study has several limitations to be acknowledged. The limited size of the population precludes reliable multivariable analyses, and the dependency of strain analyses on good image quality may have influenced the results. Notably, small intercostal spaces in very thin patients might worsen imaging definition, especially of the basal LV portions, therefore potentially providing lower strain values before re-feeding. As reported in other studies,[20] regional strain measures have inter-vendor and inter-operator, and intra-operator variability. However, in our study, all exams were performed by the same operator with the same device. The large number of examinations compensates, at least in part, for intra-operator variability. Despite these limitations, we are convinced that our observations are at least a hypothesis-generating study, suggesting that GLS measurement may be clinically valuable to identify early patients with AN at higher risk of developing myocardial dysfunction. We found that GLS is remarkably altered in patients with AN of adult age and that more severe cases have a basal blue (i.e., dysfunctioning) pattern at bull's eye mapping that appeared reversible with improved feeding. However, further studies are necessary to understand the pathophysiological mechanism leading from malnourishment to systolic myocardial dysfunction.

Disclosures

The authors have no conflicts of interest to declare.

Acknowledgment

The authors are grateful to "Fondazione A.R. Card Onlus" for its unconditional support.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author

Ethical approval

The study was approved by the local Ethics Committee (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana, Sezione: Area Vasta Centro), which, in keeping with statements by the Italian Regulatory Authorities for observational studies (*https://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552*), granted a waiver of informed consent from study participants.

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