The association of cardiac function, structure, and glycemic control in patients with old myocardial infarction: a study using cardiac magnetic resonance

Junko Hamai^{1,2} · Akinobu Nakamura³ · Shingo Kato⁴ · Yasuo Terauchi²

Received: 16 December 2015 / Accepted: 19 April 2016 / Published online: 6 May 2016
© The Japan Diabetes Society 2016

Abstract

Purpose Cardiac magnetic resonance imaging (MRI) can provide noninvasive and accurate quantitative assessment of the left ventricular (LV) structure and function. We investigated the association between LV MRI measures and glycemic control in patients with old myocardial infarction (OMI).

Materials and methods The study population consisted of 51 OMI patients. By using a 1.5-T MRI scanner, we acquired cine MRI and late gadolinium-enhanced MRI. We calculated the LV volume, LV mass (LVM), LV function and percentage of infarcted myocardial volume over the total LV myocardial volume (%LGE). Patients were allocated to three groups: normal glucose tolerance (NGT), $n = 9$; impaired glucose tolerance (IGT)/impaired fasting glucose (IFG), $n = 15$; diabetes mellitus (DM), $n = 27$; respectively.

Results LVM was significantly increased in the DM group compared with the NGT group ($p = 0.002$). Multiple linear regression analysis demonstrated that HbA1c levels were significantly and independently associated with LVM after

adjustment for risk factors of congestive heart failure and %LGE ($p = 0.009$). The LV ejection fraction (EF) was not associated with HbA1c levels.

Conclusion Our findings suggest that glucose tolerance in patients with OMI may be associated with LV wall thickness. LVM calculation by cine MRI might be useful for longitudinal follow-up of the effect of diabetic treatment on OMI patients.

Keywords Glycemic control · Old myocardial infarction · Left ventricular mass · HbA1c

Introduction

Recent studies such as ACCORD [1], ADVANCE [2] and VADT [3] have shown that intensive glucose control does not prevent macrovascular complications in patients with diabetes mellitus (DM). A subgroup analysis of the ACCORD [1] study even suggested that intensive glycemic control may be associated with increased risk of mortality in diabetic patients with high cardiovascular risk. Furthermore, congestive heart failure is more prevalent [4] and one of the important causes of death in diabetic patients with old myocardial infarction (OMI) [5–7]. Apart from the existing data for cardiovascular events, the importance of glycemic control in the prognosis of patients after myocardial infarction is unclear. Very few reports have studied diabetic OMI patients. Assessment of left ventricular (LV) structural change and function with a highly reproducible method would be advantageous for clinical management in diabetic OMI patients.

Cardiac magnetic resonance imaging (MRI) has emerged as a noninvasive and accurate modality for the assessment of cardiac morphology and function. Cine MRI

✉ Yasuo Terauchi
terauchi@yokohama-cu.ac.jp

¹ Division of Endocrinology and Diabetes, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama 236-0051, Japan

² Department of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan

³ Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

⁴ Department of Cardiology, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, Yokohama 236-0051, Japan

provides more reproducible evaluation of LV volume and function in comparison to echocardiography [8]. For the detection of myocardial infarction, the accuracy of late gadolinium-enhanced (LGE) MRI is superior to conventional scintigraphy [9]. In addition, LGE MRI enables the quantitative evaluation of myocardial infarction with excellent reproducibility. Importantly, the severity of myocardial infarction on LGE MRI has been shown to be a strong prognostic factor for patients with coronary artery disease [10, 11]. We hypothesized that assessment by cardiac MRI may demonstrate a strong association between glycemic control and LV morphological abnormality in OMI patients.

Here we performed a cross-sectional study of glucose tolerance, LV structure and LV function in OMI patients using cardiac MRI as a highly accurate method to evaluate the cardiac morphology and function.

Materials and methods

Patient selection

We researched all patients treated by cardiologists at the Kanagawa Cardiovascular and Respiratory Center who underwent cardiac MRI and evaluated them for glucose tolerance (who were already diagnosed as having type 2 diabetes) using the 75-g oral glucose tolerance test from August 2008 to May 2012. Patients with angina pectoris and AMI were excluded from the study as in these patients the left ventricular function is changing and, to a large extent, depends on the duration since the onset of AMI. Casual blood glucose and HbA1c measurements were performed for all study participants. Plasma glucose, lipids and creatinine were measured using routine automated laboratory techniques. The value of HbA1c (%), equivalent to the internationally used HbA1c (%) [HbA1c (NGSP)] defined by the NGSP (National Glycohemoglobin Standardization Program), was expressed by adding 0.4 % to HbA1c (JDS) (%) as defined by the Japanese Diabetes Society (JDS) [12].

Patients diagnosed with hypertension were defined as those receiving pharmacological treatment for hypertension or systolic blood pressure (BP) of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg. Patients diagnosed with dyslipidemia were those undergoing pharmacological therapy for dyslipidemia or with the following blood test results: triglycerides ≥ 150 mg/dl and/or high-density lipoprotein cholesterol < 40 mg/dl and/or low-density lipoprotein cholesterol > 140 mg/dl.

Preexisting diabetes was defined as known DM treated by either diet and lifestyle interventions or an additional oral glucose-lowering medication and insulin. The patients

without preexisting diabetes underwent the oral glucose tolerance test and were classified into three groups: (1) normal glucose tolerance (NGT); (2) impaired fasting glucose (IFG) or impaired glucose tolerance (IGT); (3) DM according to the Guidelines of American Diabetes Association [13]. This study did not include type 1 diabetes patients. This study was approved by the Ethics Committee of Kanagawa Cardiovascular and Respiratory Center.

Cardiac MRI acquisition

MRI was performed on a 1.5-T MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands) with a 32-channel cardiac coil. Cine and LGE MRI images were acquired in all study participants.

Electrocardiographic monitoring leads were positioned on supine patients and then imaging started. Vertical and horizontal long-axis cine MRI images of the LV were acquired with a steady-state free precession sequence. LV volumetric and functional measures including the end diastolic volume, end systolic volume, stroke volume, left ventricular mass (LVM) and LV ejection fraction (EF) were calculated from short-axis cine MR images. Cine MR imaging parameters were as follows: echo time (TE) 1.7 ms; reception time (TR), 4.1 ms; flip angle (FA), 55°; field of view (FOV), 350 × 350 mm; acquisition matrix, 128 × 128; slice thickness, 10 mm; the number of phases per cardiac cycle, 20. After scanning of cine MRI, the patients were injected with 0.15 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer Healthcare, Leverkusen, Germany). LGE images were acquired in the same views 10–15 min later using an inversion recovery-prepared gradient-echo sequence. The imaging parameters for LGE MRI were as follows: TR, 4.3 ms; TE, 1.3 ms; FA, 15°; FOV, 380 × 380 mm; acquisition matrix, 256 × 180; slice thickness, 10 mm. The null point of the normal myocardium was determined using a Look-Locker sequence.

Image analysis

Data were analyzed with a commercial workstation (Extended MR Workspace, version R4.2, Philips Healthcare). To calculate the LVM, the epi- and endocardial LV borders were manually traced on short axis cine stacks. The LVM was calculated as the sum of the myocardial volume multiplied by the specific gravity (1.05 g/ml) of myocardial tissue [14]. The infarcted myocardial volume was measured by using a manual tracing method on LGE short axis slices as previously described [15] (Fig. 1). We calculated the percentage of infarcted myocardial volume over the total LV myocardial volume (%LGE) using the following formula.

Fig. 1 Quantitative analysis of infarcted myocardium using LGE MRI. **a, b** Short axis slice of the LGE MRI image from an inferior OMI patient. Infarcted myocardium is displayed as the *white region* (red arrows). We drew contours in the endocardial border (green line) and epicardial border (yellow line). Segmentation was performed by

putting a pink-colored wheel on the LGE MRI image. **c** Non-infarcted myocardium is shown as the *blue region*; infarcted myocardium is demonstrated as the *red region*. %LGE was automatically calculated on the software

$$\% \text{ LGE} = \frac{\text{infarcted myocardial volume (mL)}}{\text{total LV myocardial volume (mL)}} \times 100$$

Statistical analysis

Data analyses were performed using the SPSS PC programs (version 3.1, SPSS, Inc., Chicago, IL, USA). To confirm that the data are satisfying the normal distribution, we confirmed the histogram distribution and performed the Shapiro-Wilk test. Since the Shapiro-Wilk test for LVM was statistically significant ($p = 0.022$), we used logarithmic transformation (Shapiro-Wilk, $p = 0.96$). The results for continuous variables were provided as mean $\pm$ standard deviation (SD). Categorical values were expressed as number (%). The differences among the groups (NGT, IGT or IFG, and DM) were assessed by one-way analysis of variance (ANOVA) or chi-square analysis. If the result of ANOVA was statistically significant, we employed a t test as a post hoc analysis for comparing the groups. Univariate and multivariate statistics were used to investigate the association of the LV structure and function with the HbA1c level. All probability values were two-sided, and the value of $p < 0.05$ was considered to be statistically significant.

Results

A total of 78 patients were identified. Of these, 27 patients were not included based on the exclusion criteria (AMI 9 patients; angina pectoris 18 patients). A total of 51 patients were included. Clinical and biochemical characteristics for the groups with NGT, IGT or IFG, and DM are listed in

Table 1. There were 9 patients with NGT, 15 patients with IGT (13 patients) or IFG (2 patients), and 27 patients with DM. The mean HbA1c level was significantly higher in patients with DM than in those in other groups. Other parameters did not significantly differ between the groups.

Figure 2 shows boxplots of LVMlog10 in the NGT, IGT or IFG, and DM groups. There was a significant differences among the three groups ($p = 0.024$). LVM was significantly higher in the DM group than in the NGT group ($p = 0.002$). There were no significant associations between HbA1c levels and LVEF ($p = 0.264$).

Table 2 shows the results of univariate and multiple linear regression analysis between LVM and other variables. Univariate analysis shows that there was a significant positive correlation between LVM and HbA1c ($p = 0.001$) (Fig. 3) and SBP ($p = 0.036$) and a negative correlation between LVM and age ($p = 0.011$). Multiple linear regression analysis was performed for variables that were statistically significant in univariate analysis and important risk factors for left ventricular hypertrophy (LVH). LVM was independently and significantly associated with HbA1c level ($p = 0.009$), BMI ($p = 0.045$) and LGE (%) ($p = 0.021$), which was independent of hypertension and age ($R^2 = 0.453$, ANOVA $p < 0.001$). Table 3 shows the values for HbA1c and cardiac function. There was no significant correlation between HbA1c and cardiac function.

Discussion

To the best of our knowledge, ours is the first study to show that the HbA1c level is associated with LVM, even after adjusting for known risk factors. LV wall thickness is clinically important; it is one of the well-known predictors of heart failure and risk for cardiovascular morbidity and

Table 1 Clinical characteristics of study subjects

	NGT (N = 9)	IGT/IFG (N = 15)	DM (N = 27)	P value
Age (years)	70.1 ± 7.7	67.6 ± 9.0	65.3 ± 9.7	–
Sex (male/female)	9/0	15/0	25/2	0.396
BMI (kg/m ²)	24.0 ± 3.5	24.4 ± 2.9	24.5 ± 3.1	0.689
HbA1c (%)	5.2 ± 0.4	5.1 ± 0.4	6.52 ± 1.1	0.024*
SBP (mmHg)	121.3 ± 16.3	123.3 ± 9.1	128.8 ± 13.8	0.350
DBP (mmHg)	69.1 ± 12.1	73.1 ± 9.0	75.1 ± 9.5	0.116
TC (mg/dl)	172 ± 36	191 ± 28	170 ± 33	0.719
LDL-C (mg/dl)	103 ± 20	113 ± 28	104 ± 27	0.703
HDL-C (mg/dl)	50 ± 11	50 ± 17	48 ± 14	0.829
TG (mg/dl)	159 ± 115	150 ± 81	179 ± 89	0.755
Creatinine (mg/dl)	0.89 ± 0.24	0.91 ± 0.16	0.95 ± 0.21	0.687
Hypertension (%)	6 (67)	15 (100)	25 (93)	0.110
Dyslipidemia (%)	7 (78)	15 (100)	25 (93)	0.438
Smoking (%)	4 (44)	9 (60)	9 (33)	0.232
Renin-angiotensin-blocking therapy (%)	5 (56)	13 (87)	24 (89)	0.191
Statin therapy (%)	5 (56)	12 (80)	24 (89)	0.227
Beta blocker therapy (%)	3 (33)	9 (60)	16 (59)	0.516
Insulin therapy (%)	0 (0)	0 (0)	3 (11)	–
Periods after acute MI(years)	3.31 ± 4.63	4.61 ± 5.51	7.02 ± 6.93	0.987

Values are expressed as mean ± standard deviation or n (%). The difference between groups was assessed by one-way analysis of variance or chi-square test

BMI body mass index, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *NGT* normal glucose tolerance, *SBP* systolic blood pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TG* triglycerides, *MI* myocardial infarction

* Statistically significant at $p < 0.05$

Fig. 2 Boxplots showing distributions of LVMlog10 in NGT, IGT/IFG and DM subjects (ANOVA $p = 0.024^*$). *Statistically significant at $p < 0.05$. *LVM* left ventricular mass, *NGT* normal glucose tolerance, *IGT* impaired glucose tolerance, *IFG* impaired fasting glucose, *DM* diabetes mellitus

mortality [16–19], even in subjects with normal EF [20]. Although echocardiography allows for the evaluation of LVM, MRI is a more precise and reproducible method for this purpose.

Several clinical studies have reported that diabetes patients have increased LV wall thickness in comparison with nondiabetics [21, 22]. Myocardial disease caused by diabetes is known as “diabetic cardiomyopathy,” which is characterized by LVH and diastolic dysfunction [23]. Diabetic cardiomyopathy is associated with metabolic disturbances. Among these are depletion of glucose transporter 4 levels, increased free fatty acid levels, carnitine deficiency and changes in the calcium homeostasis. Myocardial fibrosis [increases in angiotensin II, insulin-like growth factor I (IGF-I) and inflammatory cytokine levels], small vessel disease (microangiopathy, impaired coronary flow reserve and endothelial dysfunction), cardiac autonomic neuropathy (denervation and alterations in myocardial catecholamine levels) and insulin resistance (hyperinsulinemia and reduced insulin sensitivity) are also observed [24]. In addition, some reports have shown that in patients with diabetes adverse tissue remodeling after MI is

Table 2 Univariate and multiple linear regression analysis of the relationship between LVMlog10 and parameters could be associated with LVM

	β	SE	95 % CI	P value
Univariate linear regression analysis				
HbA1c	0.469	0.019	0.031 to 0.108	0.001*
Age	−0.362	0.002	−0.011 to −0.001	0.011*
SBP	0.301	0.007	0.001 to 0.030	0.036*
BMI	0.289	0.002	0.000 to 0.006	0.052
LGE	0.261	0.002	0.000 to 0.006	0.070
LDL-C	0.148	0.030	0.000 to 0.001	0.331
Multiple linear regression analysis				
HbA1c	0.350	0.019	0.014 to 0.090	0.009*
Age	−0.196	0.002	−0.008 to 0.001	0.113
BMI	0.254	0.006	0.000 to 0.026	0.045*
SBP	0.219	0.001	0.000 to 0.005	0.098
LGE	0.285	0.001	0.001 to 0.006	0.021*

LVM left ventricular mass, CI confidence interval, SBP systolic blood pressure, BMI body mass index, LGE late gadolinium enhancement, LDL low-density lipoprotein

* Statistically significant at $p < 0.05$

Fig. 3 Relationship between LVMlog10 and HbA1c. LVM left ventricular mass

intensified, and LV wall thickness in diabetics after AMI is increased [25, 26].

The impaired repair mechanisms in patients with diabetes after AMI can be attributed to several factors. Among those are hyperglycemia, overproduction of reactive oxygen species (ROS), accumulation of advanced glycation end products (AGEs) or high glycolysis involved in the inhibition of the vascular repair mechanisms including hypoxia-related signaling, inflammatory balance, and bone marrow-derived cell mobilization and angiogenic potential [27]. Our data corroborate the results of these investigations. Also, our study shows that LVM was correlated with

Table 3 Univariate analysis of the relationship between HbA1c and parameters of cardiac function

	β	SE	95 % CI	P value
LVEF	−0.169	1.802	−5.762 to 1.486	0.241
LVEDV	0.197	6.734	−4.184 to 22.895	0.171
LVESV	0.160	6.793	−5.952 to 21.349	0.263
LVS SV	0.157	2.050	−1.858 to 6.387	0.275

CI confidence interval, LVEF left ventricular ejection fraction, LVEDV left ventricular end diastolic volume, LVESV left ventricular end systolic volume, LVS SV left ventricular stroke volume

BMI and LGE (Table 2). Previous studies have reported that BMI was correlated with increased LVM [28] and that larger infarct size causes LVH [29]. These reports were in agreement with our results.

We found no significant association between EF and glucose intolerance, and several clinical studies have reported similar results [30–32]. Melchior et al. reported that diabetes is associated with long-term mortality after AMI; this was independent of either left or right ventricular EF [33]. Their study indicates the importance of diastolic dysfunction associated with impaired glucose tolerance. To diagnose left ventricular diastolic dysfunction, echocardiographic evaluation is required [34]. Unfortunately, we could not evaluate diastolic dysfunction in this study. Therefore, further investigation should be needed in the future. The results of our study differ in several respects from those of the previous studies. Several clinical studies have shown that LVM is independently associated with BP [31]. However, in our study, we did not find a significant correlation between BP and LVM. In our study, most patients have hypertension and receive antihypertensive

therapy. Because BP was in a good range in the subjects of this study, it was not appropriate to consider the effect of BP on LVM. Our findings suggest that glucose tolerance in patients with OMI may be associated with LV wall thickness; these results should stimulate further research in this field. Elucidation of the extent to which glucose intolerance or glycemic control affects the LV wall thickness in patients with OMI may significantly improve the management of high-risk patients.

There are several limitations to this study. First, our results are based on a small patient population, which increases the probability of type 1 error. Second, this was a cross-sectional study. This type of study is appropriate for screening hypotheses; however, in this case, it was impossible to determine whether glucose intolerance preceded or followed an increase in LV wall thickness. To address this, we need to perform a prospective intervention study with a large number of patients.

In conclusion, LVM was higher in the DM group than in the IGT/IFG and NGT groups. LVM was significantly and independently associated with HbA1c levels in patients with OMI. This association was independent of hypertension, hyperlipidemia, BMI, age and LGE, whereas there was no significant correlation between HbA1c levels and cardiac function. Examination of the LVM may be useful in evaluating the effect of diabetes or glycemic control on cardiac disease after AMI.

Acknowledgments Statistical analyses in this study were supported by Kentaro Sakamaki at Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan.

Compliance with ethical standards

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent is not necessarily required for observational studies using existing data.

Conflict of interest Y. T. has received lecture fees from MSD, Ono Yakuhin, Boehringer Ingelheim, Takeda, Tanabe Mitsubishi, Daiichi-Sankyo, Sanwa Kagaku Kenkyusho, Novo Nordisk, Eli Lilly, Sanofi, Dainippon-Sumitomo, Shionogi, Bayer Yakuhin, Astellas, AstraZeneca and Taisho Toyama as well as scholarship grants from MSD, Ono Yakuhin, Boehringer Ingelheim, Takeda, Tanabe Mitsubishi, Daiichi-Sankyo, Sanwa Kagaku Kenkyusho, Novo Nordisk, Eli Lilly, Sanofi, Dainippon-Sumitomo, Shionogi, Bayer Yakuhin, Astellas, AstraZeneca and Taisho Toyama. The other authors declare that they have no conflict of interest.

References

- Gerstein HC, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Eng J Med*. 2008;358:2545–59.
- Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Eng J Med*. 2008;358:2560–72.
- Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Eng J Med*. 2009;360:129–39.
- Dhingra R, Vasan RS. Diabetes and the risk of heart failure. *Heart Fail Clin*. 2012;8:125–33.
- Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following MI in men versus women: the Framingham study. *JAMA*. 1988;260:3456–60.
- Mak KH, Topol EJ. Emerging concepts in the management of acute MI in patients with diabetes mellitus. *J Am Coll Cardiol*. 2000;35:563–8.
- Dandamudi S, Slusser J, Mahoney DW, Redfield MM, Rodeheffer RJ, Chen HH. The prevalence of diabetic cardiomyopathy: a population-based study in Olmsted County, Minnesota. *J Card Fail*. 2014;20:304–9.
- Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29–34.
- Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet*. 2003;361:374–9.
- Bülow H, Klein C, Kuehn I, et al. Cardiac magnetic resonance imaging: long term reproducibility of the late enhancement signal in patients with chronic coronary artery disease. *Heart*. 2005;91:1158–63.
- Zemrak F, Petersen SE. Late gadolinium enhancement CMR predicts adverse cardiovascular outcomes and mortality in patients with coronary artery disease: systematic review and meta-analysis. *Prog Cardiovasc Dis*. 2011;54:215–29.
- Seino Yutaka, Nanjo Kishio, Tajima Naoko, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest*. 2010;1:212–28.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2012;35(Supple 1):S64–71.
- Semelka RC, Tomei E, Wagner S, et al. Normal left ventricular dimensions and function: interstudy reproducibility of measurements with cine MR imaging. *Radiology*. 1990;174:763–8.
- Yoon YE, Kitagawa K, Kato S, et al. Prognostic significance of unrecognized myocardial infarction detected with MR imaging in patients with impaired fasting glucose compared with those with diabetes. *Radiology*. 2012;262:807–15.
- Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Eng J Med*. 1990;322:1561–6.
- Westerhout CM, Lauer MS, James S, Fu Y, Wallentin L, Armstrong PW. Electrocardiographic left ventricular hypertrophy in GUSTO IV ACS: an important risk marker of mortality in women. *Eur Heart J*. 2007;28:2064–9.
- Taylor TR, Kamarck TW, Dianozumba S. Cardiovascular reactivity and left ventricular mass: an integrative review. *Ann Behav Med*. 2003;26:182–93.
- Gosse P. Left ventricular hypertrophy the problem and possible solutions. *J Int Med Res*. 2005;33(S1):3A–11A.
- Turakhia MP, Schiller NB, Whooley MA. Prognostic significance of increased left ventricular mass index to mortality and sudden death in patients with stable coronary heart disease (from the Heart and Soul Study). *Am J Cardiol*. 2008;102:1131–5.
- Lindman BR, Arnold SV, Madrazo JA, et al. The adverse impact of diabetes mellitus on left ventricular remodeling and function in

- patients with severe aortic stenosis. *Circ Heart Fail.* 2011;4:286–92.
22. Devereux RB, Roman MJ, Paranicas M. Impact of diabetes on cardiac structure and function the strong heart study. *Circulation.* 2000;101:2271–6.
 23. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation.* 2007;115:3213–23.
 24. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev.* 2004;25:543–67.
 25. Greer JJ, Ware DP, Lefer DJ. Myocardial infarction and heart failure in the db/db diabetic mouse. *Am J Physiol Heart Circ Physiol.* 2006;290:H146–53.
 26. Shah AM, Hung CL, Shin SH, et al. Cardiac structure and function, remodeling, and clinical outcomes among patients with diabetes after myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both. *Am Heart J.* 2011;162:685–91.
 27. Howangyin KY, Silvestre JS. Diabetes mellitus and ischemic diseases: molecular mechanisms of vascular repair dysfunction. *Arterioscler Thromb Vasc Biol.* 2014;34:1126–35.
 28. Cuspidi C, Rescaldani M, Sala C, Grassi G. Left-ventricular hypertrophy and obesity: a systematic review and meta-analysis of echocardiographic studies. *J Hypertens.* 2014;32(1):16–25.
 29. Małek ŁA, Spiewak M, Kłopotowski M, et al. Influence of left ventricular hypertrophy on infarct size and left ventricular ejection fraction in ST-elevation myocardial infarction. *Eur J Radiol.* 2012;81(3):e177–81.
 30. Melchior T, Gadsbøll N, Hildebrandt P, Køber L, Torp-Pedersen C. Clinical characteristics, left and right ventricular ejection fraction, and long-term prognosis in patients with non-insulin-dependent diabetes surviving an acute myocardial infarction. *Diabet Med.* 1996;13:450–6.
 31. Palmieri V, Bella JN, Arnett DK, et al. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: hypertension Genetic Epidemiology Network (HyperGEN) study. *Circulation.* 2001;103:102–7.
 32. Goldweit RS, Borer JS, Jovanovic LG, et al. Relation of hemoglobin A1 and blood glucose to cardiac function in diabetes mellitus. *Am J Cardiol.* 1985;56:642–6.
 33. Lamas GA. Left ventricular hypertrophy in post - myocardial infarction left ventricular remodeling and in hypertension; similarities and contrasts. *Eur Heart J.* 1993;14:15–21.
 34. Paulus WJ, Tschope 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 and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J.* 2007;28(20):2539–50.