



Basic Study

Right ventricular dysfunctions in type 1 diabetic mice: A longitudinal study

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Abstract

BACKGROUND

Diabetes has become a widespread metabolic disease affecting multiple organs. Among diabetic complications, cardiovascular complications are the main cause of patient morbidity and mortality. Diabetic cardiomyopathy is a diabetes-specific cardiomyopathy in the absence of other cardiovascular disease and occurs more frequently in type 1 diabetes (T1D) than in type 2 diabetes. Previous studies on diabetic cardiomyopathy have predominantly focused on the effects of diabetes on left ventricular (LV) dysfunction, while studies of right ventricular (RV) dysfunction have been sparse but are gaining attention. Although T1D accounts for only 5%-10% of the total diabetic population, diabetic cardiomyopathy is a major cause of morbidity and mortality in children with life-long, long-term complications.

AIM

To evaluate longitudinal RV and LV functional changes in female transgenic OVE26, T1D mice and wild-type FVB mice over a 30-week period.

METHODS

RV and LV structure and function were evaluated by transthoracic echocardiography. RV systolic pressure was measured by a transducer-tipped pressure catheter. Sirius-red staining was used to quantify collagen and fibrosis, wheat germ agglutinin staining was utilized to measure cardiomyocyte size, and quantitative real-time polymerase chain reaction and Western blotting were used to quantify miRNA expression and protein abundance, respectively.

RESULTS

RV systolic function, measured by tricuspid valve annular plane systolic excursion and RV systolic velocity, was similar between control and T1D mice, but LV systolic function decreased in T1D mice at 30 weeks of age. RV diastolic dysfunction in T1D mice significantly increased by 18 weeks and progressed until 30 weeks, while LV diastolic dysfunction trended towards abnormal at 12 weeks, significantly increased by 18 weeks, and continued to progress by 30 weeks. Furthermore, RV diastolic dysfunction was accompanied by RV cardiac fibrosis and hypertrophy in T1D mice, occurring later than that in the LV. Pulmonary arterial hypertension developed in T1D mice, evidenced by increased pulmonary acceleration time to pulmonary ejection time ratio and increased RV peak systolic pressure at 30 weeks. These results suggest the development of early LV diastolic dysfunction followed by LV systolic dysfunction and RV diastolic dysfunction at 30 weeks in T1D mice.

CONCLUSION

RV diastolic dysfunction develops later than LV dysfunction in OVE26 T1D mice. Mild pulmonary arterial hypertension appear at later stages of T1D and could contribute to RV systolic impairment and remodeling.

Key Words: Diabetic cardiomyopathy; Type 1 diabetes; Right ventricle; Left ventricle; Cardiac remodeling; Cardiac dysfunction

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Core Tip: Diabetic cardiomyopathy is a diabetes-associated complication. However, the temporal relationship between right ventricle (RV) and left ventricle (LV) systolic/diastolic functions in diabetes has not been explored. Therefore, we examined longitudinal RV and LV function changes in transgenic OVE26 type 1 diabetes (T1D) mice and wild-type FVB mice over a 30-week period. T1D mice developed early LV diastolic dysfunction, followed by LV systolic dysfunction and RV diastolic dysfunction at 30 weeks. Furthermore, T1D mice demonstrated an increase in the pulmonary acceleration time to pulmonary ejection time ratio and RV peak systolic pressure at 30 weeks, suggesting the development of mild pulmonary arterial hypertension.

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INTRODUCTION

Diabetes has become a widespread metabolic disease that affects multiple organs. According to the International Diabetes Federation, diabetes affects an estimated 537 million adults worldwide and 783 million people will have diabetes globally by 2045[1-3]. Type 1 diabetes (T1D) arises from insulin deficiency due to an autoimmune response against pancreatic β -cells, while type 2 diabetes (T2D) is characterized by peripheral insulin resistance. Although T1D accounts for only 5%-10% of the total diabetic population, it is a major cause of morbidity and mortality in children who suffer life-long, long-term complications[4]. Among diabetic complications, cardiovascular complications are the main cause of patient morbidity and mortality. Numerous studies have confirmed a higher prevalence of heart failure (HF) in diabetic patients (11.8%-28%) compared to nondiabetic patients (3.2%-4.5%)[5-8]. In T1D and T2D, cardiac complications account for 44% and 52% of mortality, respectively[9]. Diabetic cardiomyopathy (DCM) is a form of cardiomyopathy specific to diabetes, occurring in the absence of coronary artery disease, hypertension or other cardiovascular conditions[10,11]. Previous studies of DCM have primarily focused on the effects of diabetes or prediabetes on left ventricular (LV) dysfunction, whereas research on right ventricular (RV) dysfunction has been limited but is now gaining increased attention[12,13].

Many factors, including hyperglycemia, insulin resistance and other comorbidities can contribute to LV pathogenesis and dysfunction in diabetic individuals. Like the LV, diabetes-mediated RV injury can occur from direct diabetic effects. Additionally, the RV may be significantly affected by LV/RV ventricular interaction[14] and pulmonary arterial hypertension (PAH) secondary to diabetic pulmonary vascular damage[15-17]. These factors complicate our ability to discern which diabetes-induced RV pathogenic alterations are directly attributable to diabetes itself, as opposed to being secondary to LV dysfunction and/or PAH. Previous preclinical and clinical studies of cardiac function in diabetes have typically examined a single cross-sectional time point or assessed the RV and LV independently. The temporal relationship between RV and LV systolic/diastolic functions in diabetes has not been explored. We hypothesized that the timing and manifestation of RV and LV systolic and diastolic dysfunction differ in T1D. Therefore, we aimed to test the following questions: (1) What are the characteristics of RV systolic and/or diastolic dysfunction in a T1D model? (2) How does the time course of RV structural and functional abnormalities compare with that of the LV in T1D? and (3) What pathophysiological mechanisms underlie the distinct profiles of RV and LV dysfunction in T1D?

MATERIALS AND METHODS

Animals

The OVE26 mouse line [mouse nomenclature: FVB(Cg)-Tg(Ins2-CALM)26OveTg(Cryaa-Tag)1Ove/PneJ; JAX strain #005564; Jackson Laboratory, ME, United States] is a transgenic T1D murine model first reported in 1989. They suffer pancreatic β -cell damage by genetic calmodulin overexpression[18]. These mice spontaneously develop diabetes within the first week of life, can survive for approximately one year without insulin treatment, and maintain near normal body weight. OVE26 mice are considered an ideal animal model for long-term T1D complication study[19]. Female transgenic OVE26 mice in the FVB background and wild-type FVB mice were housed at the University of Louisville Research Resources Center in a 12-hour light/12-hour dark cycle at 22 °C. All mice had free access to a standard chow diet (autoclaved LabDiet 5010) and tap water. Female mice were used because of our previous work on DCM in female OVE26 mice[20], and OVE26 female mice develop more advanced diabetic nephropathy than male OVE26 mice[21]. The FVB control and OVE26 mice were sacrificed at 8-, 12-, 18-, 24- and 30-weeks of age after fasting overnight for 12 hours. All animal procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the University of Louisville Institutional Animal Care and Use Committee (Approval No. IACUC 24365). Mice were euthanized with intraperitoneal injection of 1.2% avertin after measurement of body weight, blood glucose and RV systolic pressure (RVSP) at 8, 12, 18, 24 and 30 weeks of age ($n = 6-8$). Hearts were collected (separated into RV/LV + septum by dissection) and stored at -80 °C after measuring their weights. Tibia length was measured and recorded.

Echocardiography

Mice were anesthetized with isoflurane (0.5% to 1.2% in 1 L/minute pure oxygen, maintained heart rate: 400-450 bpm) and cardiac function was assessed using a high-resolution transthoracic echocardiography imaging system (Vevo 2100 Imaging System; FUJIFILM Visual-Sonics, Toronto, Canada). Ultrasonic parameters were obtained to comprehensively assess RV and LV function using modified left parasternal long-axis, left parasternal short axis and apical four-chamber views.

RVSP measurement by transducer-tipped pressure catheter

Isoflurane (0.8% to 1.5% in 1 L/minute pure oxygen) was used for anesthesia induction and maintenance. Mice were placed in the supine position on a heating pad. Hair removal and sterilization were performed successively around the area of the right jugular triangle. A skin incision was made, and the right jugular vein was isolated. Venotomy was performed using microsurgical scissors after ligating the distal vein. A 1.2 F transducer-tipped pressure catheter (model FTH-1211B-0081; Transonic, London, Canada) was introduced into the right jugular vein and slowly passed into the right atrium and RV. Continuous RV pressure waves were recorded after 15 minutes of catheter acclimation. The average RVSP was collected and analyzed using standard software (LabChart Pro Software; AD Instruments, Colorado Springs, CO, United States). RV pressure waveforms were recorded for 1-2 minutes, and 30-60 waveforms in steady state were used to calculate the average value.

Histological staining

Isolated hearts were fixed in 10% formalin and dehydrated in graded alcohol, then subsequently processed with xylene, embedded in paraffin and sectioned into 5 μ m-thick specimens. Picro-Sirius red staining was used to assess cardiac collagen and fibrosis. Collagen fibers stained red compared to cardiomyocytes, which stained green. To determine myocyte size, cardiac sections were stained with fluorescein isothiocyanate-conjugated wheat germ agglutinin for 50 minutes (Alexa Fluor 488, Invitrogen, CA, United States). All images were captured with a Nikon ECLIPSE E600 microscope (Nikon Corporation, Japan) and quantitatively analyzed using Image J software.

Western blot analysis

Protein (20 μ g) isolated from either RV or LV tissues was subjected to 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gels (Bio-Rad, Hercules, CA, United States) and transferred to a polyvinylidene fluoride membrane after electrophoresis. After blocking with 5% skim milk for 1 hour, membranes were washed three times in Tris-buffered saline with Tween-20 (TBS-T), then incubated with primary antibodies overnight at 4 °C [fibronectin (FN) and connective tissue growth factor (CTGF), purchased from Abcam, Cambridge, United Kingdom; atrial natriuretic peptide (ANP) and β -actin, obtained from Santa Cruz Biotechnology, Santa, CA, United States]. Membranes were then incubated with anti-mouse or anti-rabbit secondary horseradish peroxidase-conjugated antibody (Cell Signaling Technology, Danvers, MA, United States) for 1 hour after washing membranes with TBS-T. Bands were visualized with an ECL Kit (Bio-Rad, Hercules, CA, United States), and grayscale values were analyzed using Image Lab software (Bio-Rad, Hercules, CA, United States).

RNA isolation and quantitative real-time polymerase chain reaction

Total RNA was isolated from 8 mg RV and 15 mg LV tissue using TRIzol reagent (Invitrogen, Carlsbad, CA, United States) and quantified by a Nano-Drop ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, United States). A total of 1 μ g RNA was reverse transcribed in a total volume of 20 μ L containing 4 μ L MgCl₂, 4 μ L avian myeloblastosis virus RT 5 $\times$ buffer, 2 μ L deoxynucleoside triphosphates, 0.5 μ L ribonuclease inhibitor, 1 μ L avian myeloblastosis virus RT, 1 μ L deoxythymidine oligomer primer and nuclease-free water). Quantitative real-time polymerase chain reaction (PCR) was performed in a 10 μ L volume (5 μ L TaqMan Universal PCR Master Mix, 0.5 μ L primers, 3 μ L cDNA and 1.5 μ L nuclease-free water) using the LightCycler 96 RT-PCR system (Roche Diagnostics Corporation, Indianapolis, IN, United States). Gene-specific primers [primer for FN, CTGF, type I collagen (Col I), ANP, β -actin] were obtained from Thermo Fisher (Grand Island, NY, United States). Fold differences among samples were measured with β -actin as the endogenous reference gene.

Statistical analysis

Data are presented as mean $\pm$ SD for each variable. $P < 0.05$ was considered statistically significant. Differences between FVB and OVE26 group were assessed using an unpaired t -test. All protein and RNA values were normalized to a value of 1 in the control group. All the statistical analysis and graphs were performed and generated in GraphPad Prism 8 Software (GraphPad Software, San Diego, CA, United States).

RESULTS

Characterization of FVB and OVE26 mice

Total body weight was higher in OVE26 mice compared to age-matched FVB mice (Figure 1A). While fasting blood glucose levels were within the normal range for all wild-type FVB mice, OVE26 mice exhibited hyperglycemia from 8 weeks of age to 30 weeks of age (Figure 1B).

Dynamic changing trends of RV and LV dysfunctions in OVE26 mice

We used echocardiography to determine changes in RV and LV function in OVE26 mice and control mice. Compared with FVB mice, OVE26 mice demonstrated similar LV ejection fraction and LV fractional shortening from 8 weeks to 24 weeks, but both values were significantly reduced at 30 weeks of age (Figure 1C and D). Compared to the LV, RVSP in the OVE26 group was normal in mice ranging from 8-weeks-old to 30-weeks-old. There was no significant difference between FVB and OVE26 mice in tricuspid annular plane systolic excursion and RV systolic velocity at any time-point examined (Figure 1E and F). One measure of LV diastolic dysfunction, the mitral valve E-to-E' ratio, trended abnormally at 12 weeks and was significantly increased in OVE26 mice compared to controls from 18 weeks to 30 weeks (Figure 2A).

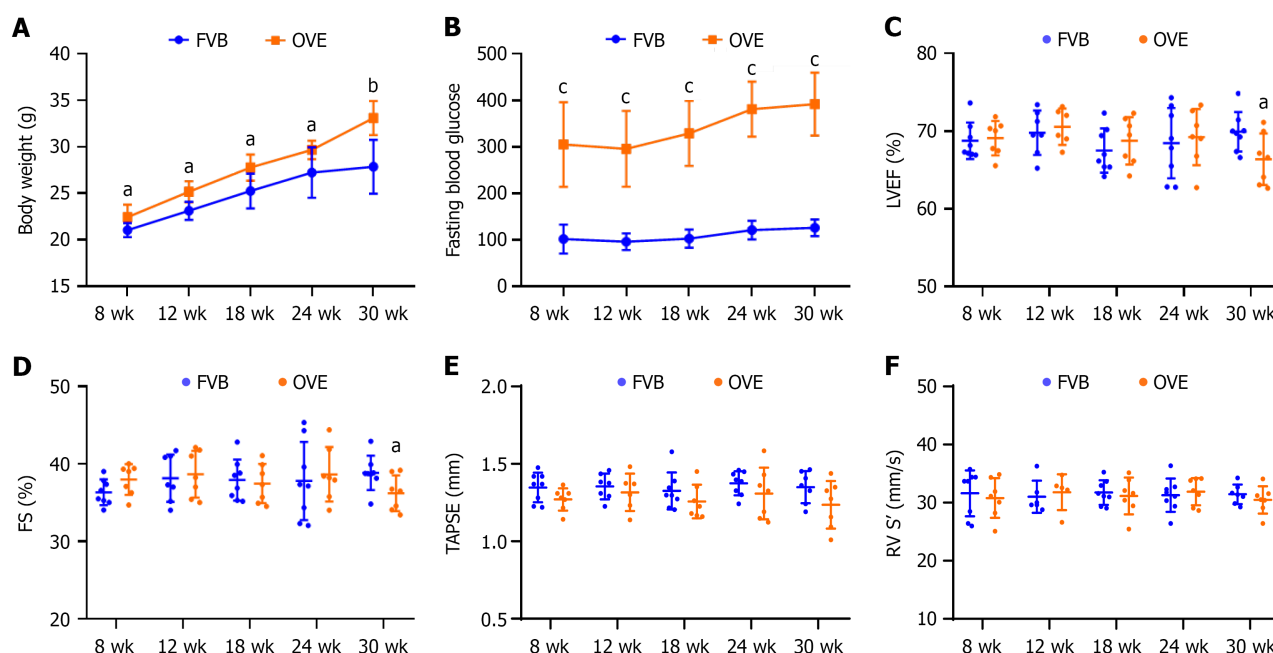


Figure 1 General features and cardiac functions of OVE26 vs control FVB mice. A: Body weight; B: Fasting blood glucose; C: Left ventricle ejection fraction; D: Left ventricle fractional shortening; E: Right ventricle tricuspid valve annular plane systolic excursion; F: Right ventricle systolic velocity. Data are presented as mean $\pm$ SD (*n* = 6-8). ^a*P* < 0.05 vs control FVB mice; ^b*P* < 0.01 vs control FVB mice; ^c*P* = 0.06 vs control FVB mice. LVEF: Left ventricle ejection fraction; FS: Fractional shortening; TAPSE: Tricuspid valve annular plane systolic excursion; RV S': Right ventricle systolic velocity.

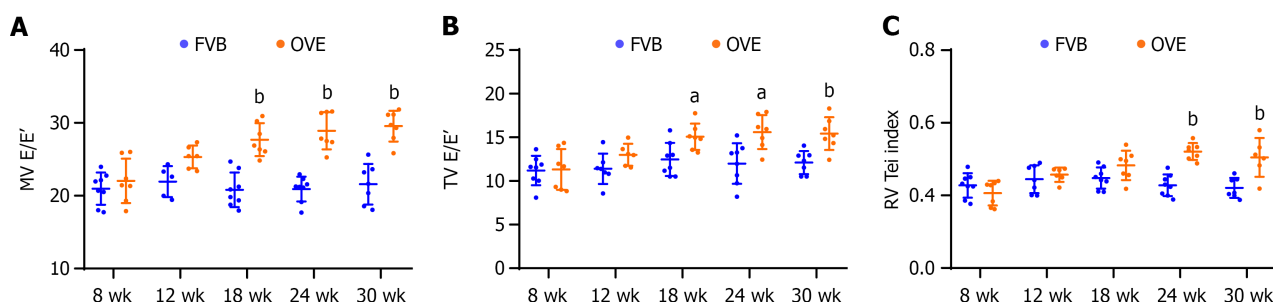


Figure 2 Left ventricular and right ventricular diastolic function in OVE26 mice vs FVB control. A: Mitral valve E-to-E' ratio for left ventricular diastolic dysfunction; B: Tricuspid valve E-to-E' ratio for right ventricular diastolic dysfunction; C: Right ventricular myocardial performance index (right ventricular Tei index). Data are presented as mean $\pm$ SD (*n* = 6-8). ^a*P* < 0.05 vs control FVB mice; ^b*P* < 0.01 vs control FVB mice. MV E/E': Mitral valve E-to-E' ratio; TV E/E': Tricuspid valve E-to-E' ratio; RV: Right ventricular.

Similarly, one of the RV diastolic dysfunction parameters, the tricuspid valve E-to-E' ratio, significantly increased from 18 weeks to 30 weeks (Figure 2B), suggesting that RV developed diastolic dysfunction later than in the LV. Moreover, changes in Tei index, a comprehensive myocardial functional index, also indicated that OVE26 mice started to develop RV systolic and diastolic dysfunction starting at 18 weeks (Figure 2C).

The ratio of pulmonary acceleration time to pulmonary ejection time is a measure of pulmonary vascular resistance, and it first began to decrease in OVE26 mice at 24 weeks and worsened by 30 weeks, consistent with increased RVSPs in OVE26 mice at later stages (Figure 3A). Interventricular septal thickness also increased, reflecting structural changes in LV at 30 weeks in the OVE26 group (Figure 3B). Consistent with the decreased pulmonary acceleration time/pulmonary ejection time ratio, we directly measured RV peak systolic pressure *via* catheter and found that it was increased in 30-week-old OVE26 mice (Figure 3C). This confirmed that aging OVE26 mice develop PAH, concurrent with changes in the RV and the LV diastolic dysfunction.

Pathological mechanisms responsible for RV and LV dysfunction

Fibrotic responses in the RV and LV of OVE26 mice: We performed Sirius red staining to detect interstitial collagen deposition in both LV and RV tissues (Figure 4A). While heart tissues from FVB mice had minute amounts of collagen accumulation at all time-points examined, hearts from OVE26 mice had increased collagen accumulation in the LV starting at 12 weeks (Figure 4B) and the RV starting at 18 weeks (Figure 4C). These data demonstrate that myocardial fibrosis developed in both the LV and RV of OVE26 mice but the onset of LV fibrosis precedes RV fibrosis (Figure 4B and

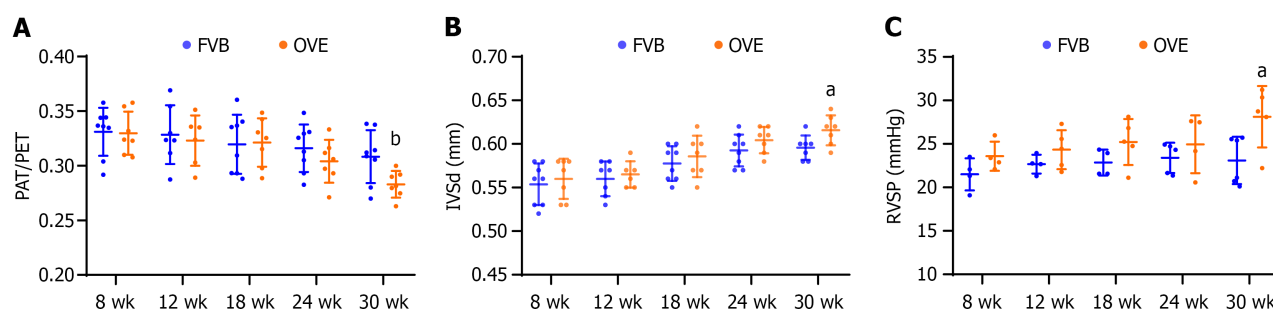


Figure 3 Index of pulmonary arterial hypertension. A: Pulmonary acceleration time/pulmonary ejection time ratio; B: Diastolic interventricular septum thickness. A and B were measured by echocardiography, data panels A and B are presented as mean $\pm$ SD ($n = 6-8$); C: Right ventricular systolic pressure was measured directly using a right ventricular pressure catheter. Data are presented as mean $\pm$ SD ($n = 4-6$). ^a $P < 0.05$ vs control FVB mice; ^b $P = 0.09$ vs control FVB mice. PAT: Pulmonary acceleration time; PET: Pulmonary ejection time; IVSd: Interventricular septum thickness; RVSP: Right ventricular systolic pressure.

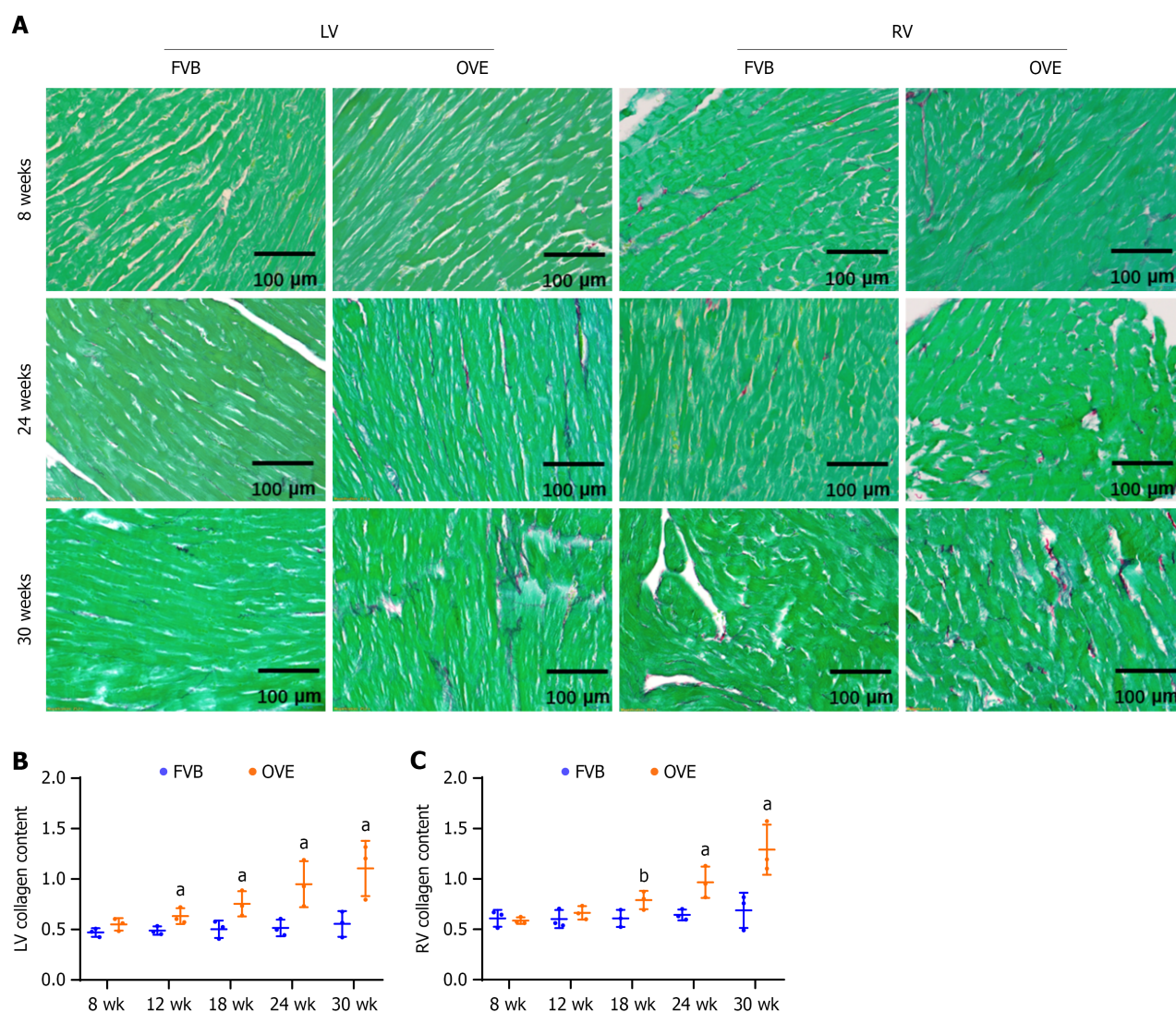


Figure 4 Fibrotic effects of type 1 diabetes on the left ventricle and right ventricle. A: Picro-Sirius red staining in left ventricle and right ventricle; B and C: Semi-quantification of cardiac collagen accumulation in left ventricle and right ventricle, respectively. Data are presented as mean $\pm$ SD ($n = 3$). ^a $P < 0.05$ vs control FVB mice; ^b $P = 0.05$ vs control FVB mice. LV: Left ventricle; RV: Right ventricle.

C). We next performed Western blotting to examine the levels of relevant proteins. FN and CTGF protein levels increased in the LV of OVE26 mice from 24 weeks (Figure 5A-D). In addition, quantitative real-time PCR analysis showed that *FN*, *CTGF*, and *Col 1* mRNA expression significantly increased in the LV of the OVE26 group from 8 weeks, normalized at 18 weeks, then increased again at the following time points (*FN* and *Col 1*: 30 weeks; *CTGF*: 24 weeks, Figure 5E-G). Only *CTGF* significantly increased by 30 weeks in the RV of OVE26 mice (Figure 6A-D). *CTGF* and *Col 1* expression increased in the RV of OVE26 mice at 18 weeks, then returned to normal and increased again at 30 weeks (Figure 6E-G). In general, mRNA level dynamics were similar but delayed in the RV compared with the LV of OVE26 mice.

Hypertrophic responses in the LV and RV of OVE26 mice

To compare cardiomyocyte size, we measured the myocyte cross-sectional area using wheat germ agglutinin staining (Figure 7A). Quantitative analysis revealed no statistical difference in cross-sectional area of the LV or RV cardiomyocytes between 8-week-old FVB and OVE26 mice. From 12 weeks, the cardiomyocytes were larger in the LV of OVE26 mice, while they were significantly larger by 18 weeks in the RV (Figure 7B and C). Western blot assays showed that ANP protein abundance increased in the LV from 12 weeks and was maintained at higher levels in the OVE26 group compared with the FVB group (Figure 8A and B), while ANP mRNA levels in the LV were significantly upregulated from 8 weeks and gradually subsided until reaching wild-type levels at 24 weeks before drastically increasing again at 30 weeks (Figure 8C). In the RV, ANP protein abundance increased from 18 weeks in OVE26 mice compared with FVB mice (Figure 8D and E). In contrast to the LV, elevated ANP mRNA expression in the RV was noted at 18 weeks and remained elevated through 30 weeks in OVE26 mice (Figure 8F).

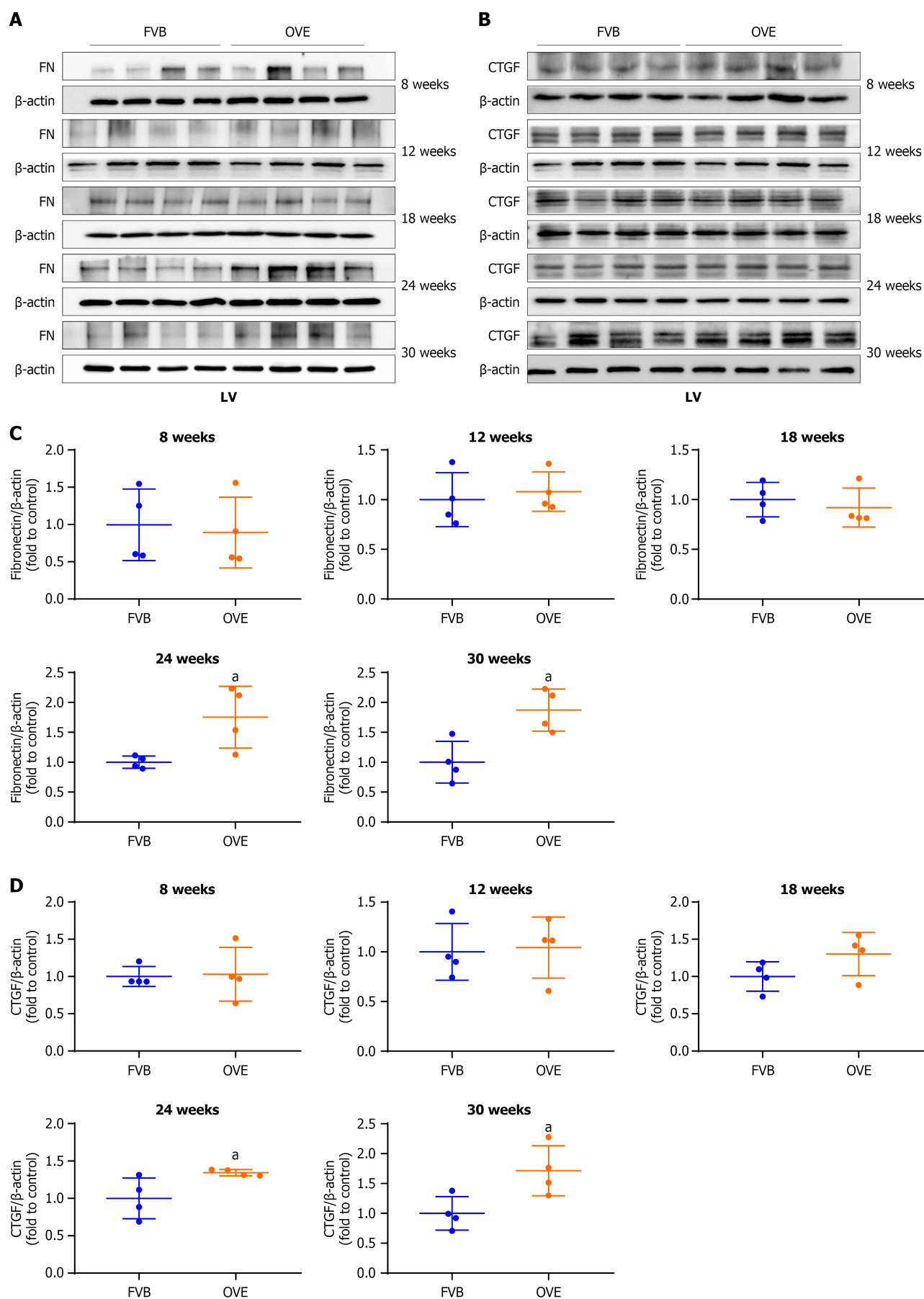
DISCUSSION

Previous studies have demonstrated that diabetes can directly cause LV systolic and diastolic dysfunction[20,22]. Subclinical LV diastolic dysfunction may occur before systolic dysfunction, which is the starting point of impaired LV function in DCM[23], consistent with the findings of our study. Diabetes-induced cardiac impairment exists as two phenotypes: HF with preserved LV ejection fraction (HFpEF), which is more prevalent in T2D with obesity characterized by metabolic derangements, and reduced LV ejection fraction, more often observed in autoimmune-prone T1D[24]. In a study by Marino *et al*[25], both T2D and T1D models were induced in C57BL/6J mice using streptozotocin, with or without pre-high-fat diet feeding. An HFpEF phenotype was observed in T2D mice but not in T1D mice. The LV E-to-E ratio, but not E/A ratio, was significantly increased in both T1D and T2D rodent models. These findings suggested that the E-to-E ratio is a good indicator of diastolic function and that early diastolic dysfunction is observed in both types of diabetes. The identification of early RV diastolic and systolic dysfunction in asymptomatic T2D patients may be important for strategies designed to limit progression[26]. Therefore, in the present study, we used E-to-E ratio to evaluate both LV and RV diastolic function.

There have been only a few studies on RV impairment in diabetes despite the significant contribution of the RV to overall cardiac function that affects DCM prognosis[27]. Recently, a large clinical study confirmed that diabetes is an independent risk factor for progressive RV dysfunction, which can cause a decline in exercise tolerance and progress to HF[28]. Research from Egypt has shown that in subclinical patients with T1D, both RV diastolic and early RV systolic dysfunction are observed with normal RV and LV ejection fraction[29]. Decreased RV and right atrial function in normotensive patients with T2D and prediabetes can be predicted using echocardiography and magnetic resonance imaging[16,30]. Therefore, RV injury and dysfunction is an essential component of pathogenic DCM development in humans and animal models of diabetes.

A single clinical trial involving 91 T2D patients with HFpEF showed dual systolic/diastolic dysfunction in the RV and pulmonary hypertension[31]. Our study evaluated RV systolic dysfunction by detecting tricuspid annular plane systolic excursion and RV systolic peak velocity of the tricuspid annulus, which measures displacement of the tricuspid valve lateral annulus and the tissue of the basal free RV wall, which are considered accurate and reproducible indicators of RV systolic function[32,33]. E-to-E ratio and Tei index are used to estimate the RV diastolic and overall RV function, respectively, by tissue Doppler imaging mode[34,35]. Existing studies are still controversial regarding the time-course and characteristic features of diabetes-induced RV dysfunction. A study of DCM in children with T1D found that both RV diastolic and systolic function were preserved, while LV diastolic function was reduced at early stages[36]. Another study on T1D adolescents with an average age of 18.2 years old showed that both RV diastolic dysfunction and RV systolic velocity measured by tissue Doppler imaging were abnormal earlier than RV ejection fraction decrease[29], which was consistent with preclinical and clinical research in T2D-induced DCM[25,37,38]. The present study found that female OVE26 mice developed RV diastolic dysfunction from 18 weeks of age, later than LV diastolic dysfunction, which presented at 12 weeks of age. LV systolic impairment was discovered at 30 weeks, while RV systolic dysfunction was still absent at the 30-week time-point, consistent with studies by Negahban *et al*[12] and Berceanu *et al*[39]. Therefore, our results suggest that: (1) RV dysfunction does not co-occur with LV dysfunction, which may imply neither RV nor LV dysfunction is solely derived from diabetic effects; and (2) The later development of RV dysfunction compared to LV dysfunction development could suggest that LV dysfunction contributes to RV dysfunction through RV/LV interdependency, as outlined in Figure 9.

Glucose levels were significantly elevated in T1D mice (Figure 1B), and because no insulin therapy was administered, the effects of glycemic control and exogenous insulin on cardiac function were not assessed in this study. In clinical settings, two-dimensional speckle-tracking echocardiography has revealed that patients with T1D can exhibit early RV systolic dysfunction despite preserved RV and LV ejection fractions[29]. However, another investigation of T1D patients



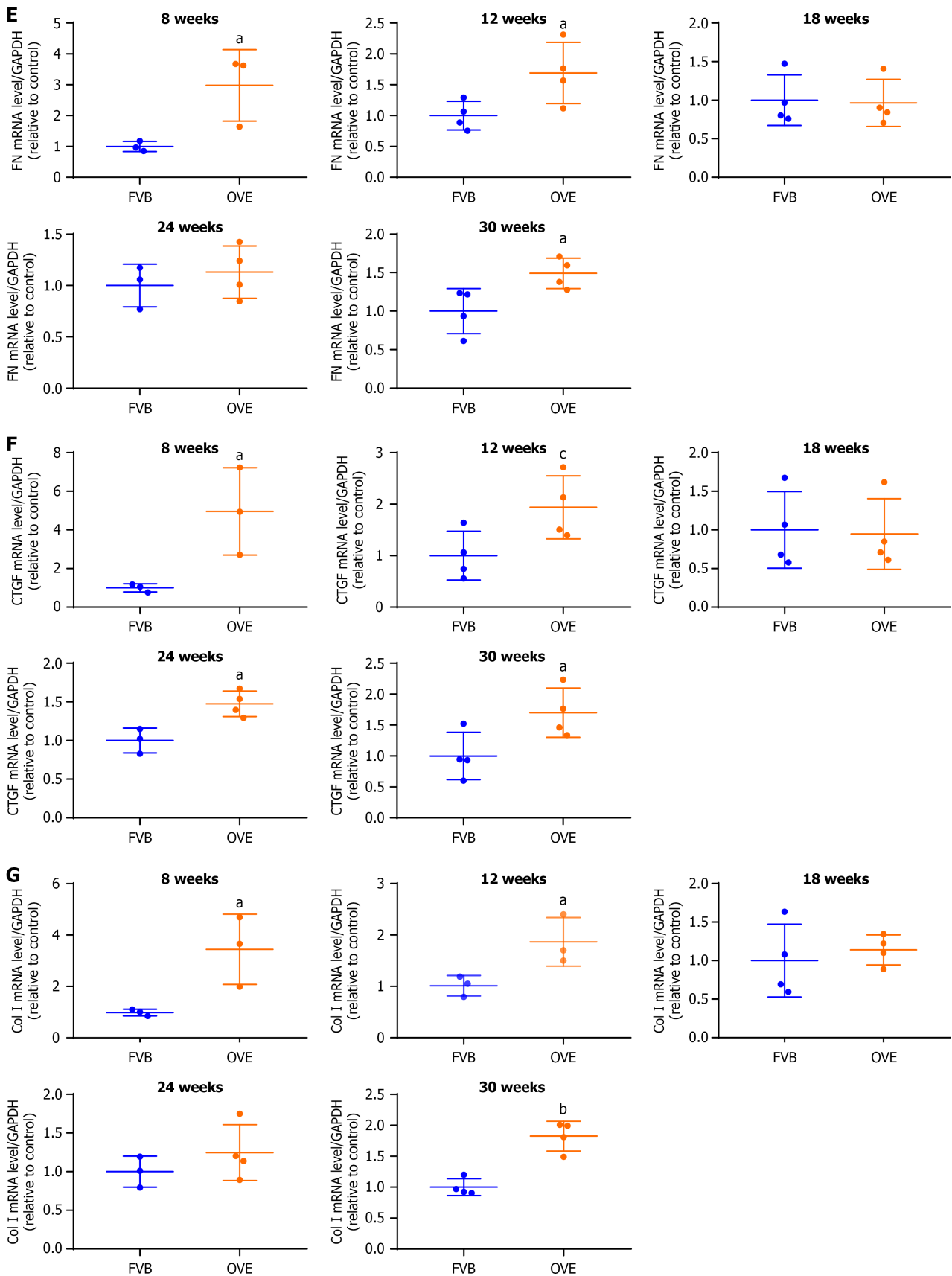
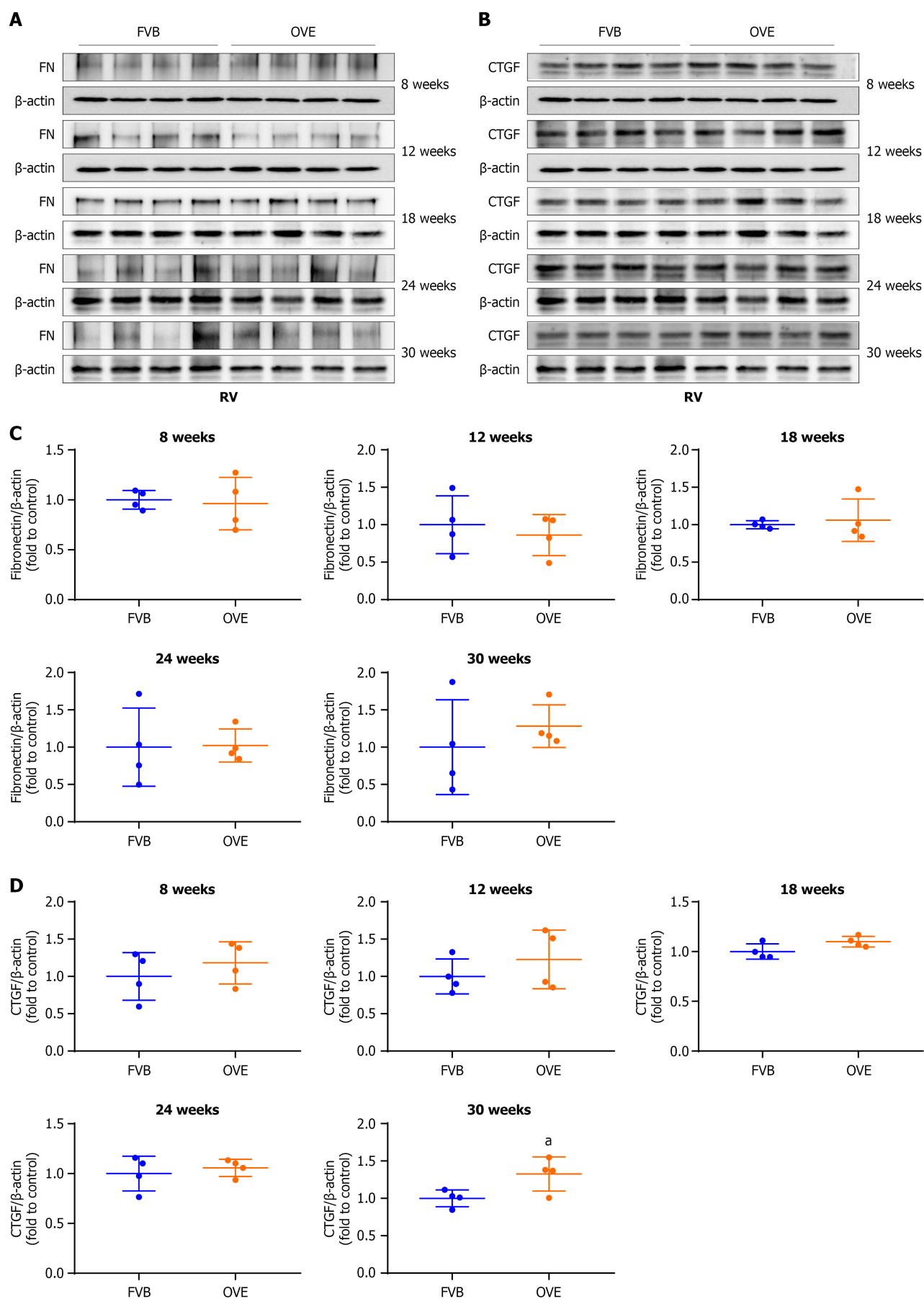


Figure 5 The impact of type 1 diabetes on cardiac fibrosis in the left ventricle of diabetic OVE26 mice. A-D: Changes in fibronectin and connective tissue growth factor protein levels in the left ventricle of 12-week-old mice were assayed by Western blot; E-G: Changes of left ventricle mRNA expression of fibronectin, connective tissue growth factor, and type I collagen were measured by quantitative reverse transcription polymerase chain reaction. Data are presented as mean $\pm$ SD ($n = 3-4$). ^a $P < 0.05$ vs control FVB mice; ^b $P < 0.01$ vs control FVB mice; ^c $P = 0.06$ vs control FVB mice. FN: Fibronectin; CTGF: Connective tissue growth factor; LV: Left ventricle; Col I: Type I collagen.



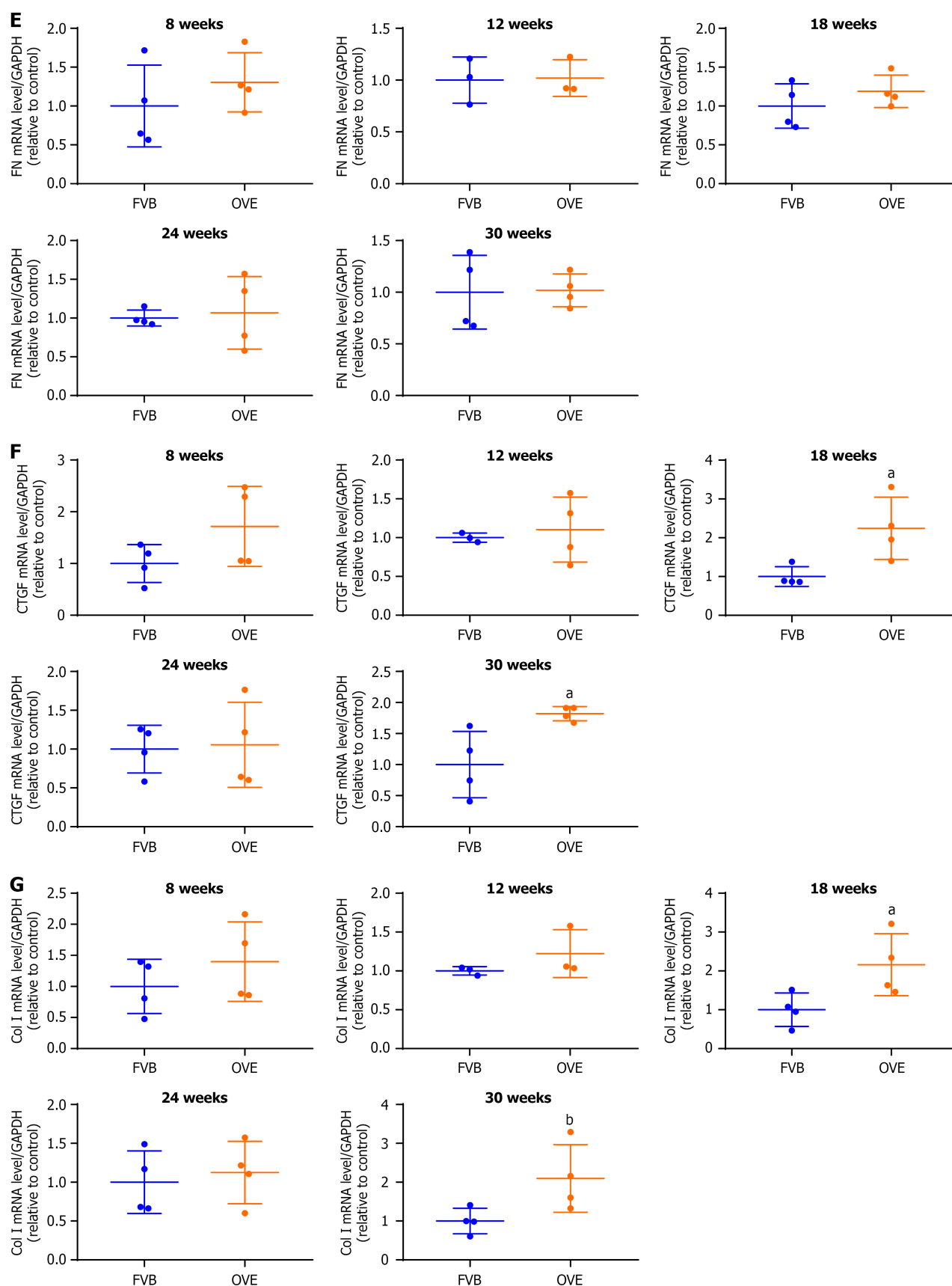


Figure 6 The impact of type 1 diabetes on cardiac fibrosis in the right ventricle of OVE26 mice. A-D: Changes in fibronectin and connective tissue growth factor protein levels in the right ventricle were assayed by Western blot; E-G: Changes of right ventricle mRNA expression of fibronectin, connective tissue growth factor, type I collagen were measured by quantitative reverse transcription polymerase chain reaction. Data are presented as mean $\pm$ SD ($n = 3-4$). ^a $P < 0.05$ vs control FVB mice; ^b $P = 0.06$ vs control FVB mice. FN: Fibronectin; CTGF: Connective tissue growth factor; RV: Right ventricle; Col I: Type I collagen.

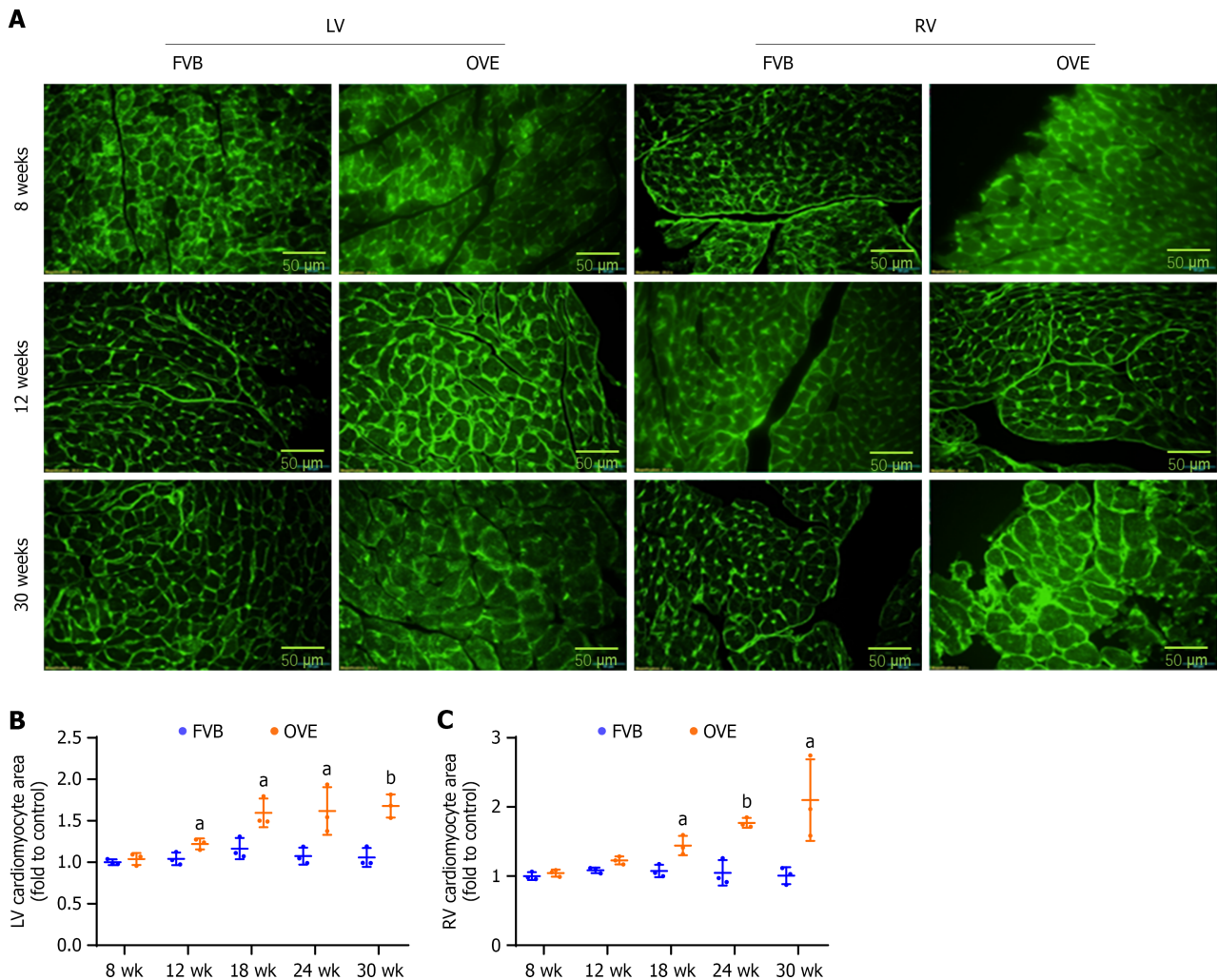
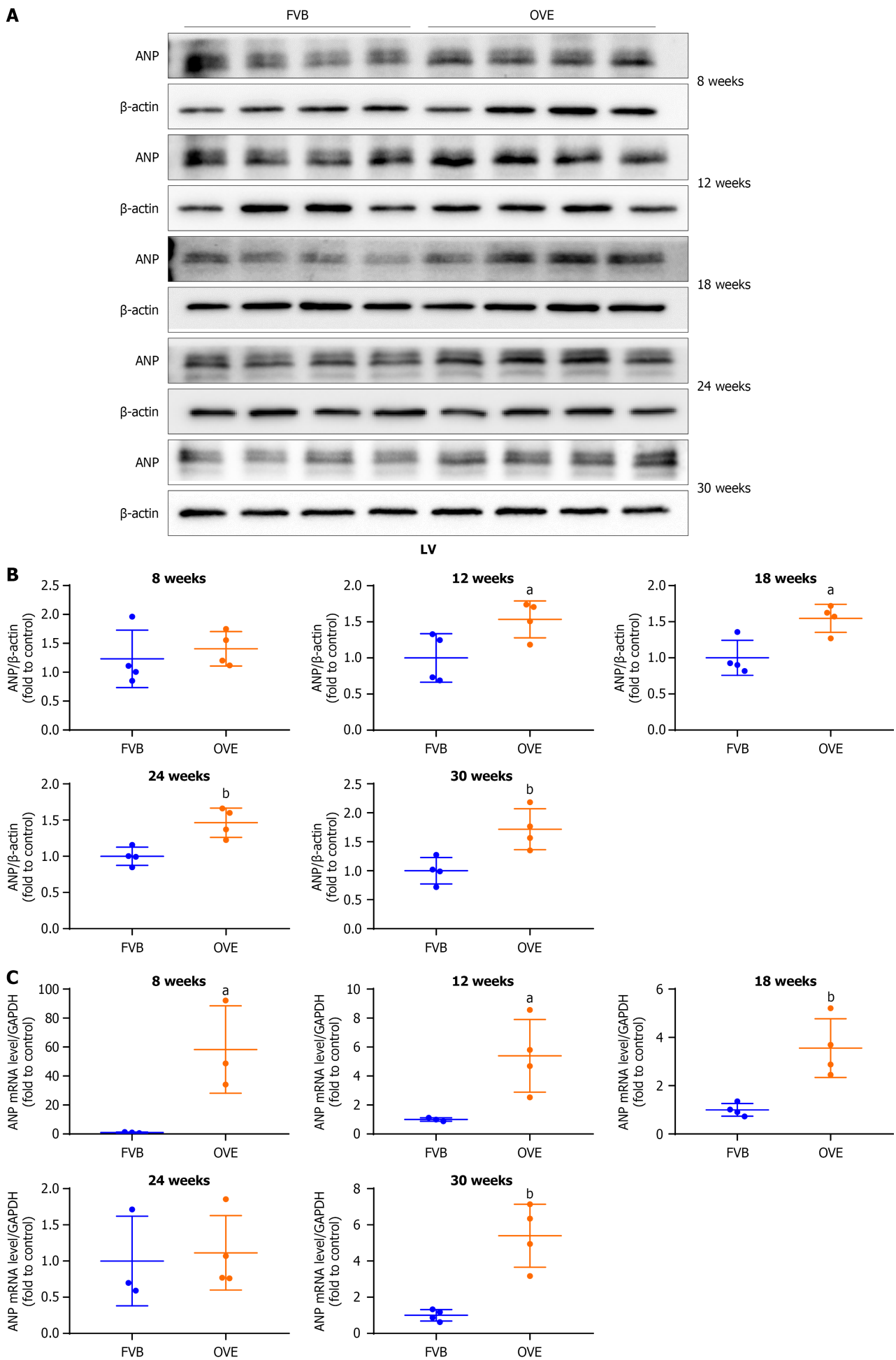


Figure 7 Changes in cardiomyocyte size in the left and right ventricles of OVE26 and FVB mice. A: Wheat germ agglutinin staining in left ventricle and right ventricle; B: Left ventricle cardiomyocyte cross-sectional area; C: Right ventricle cardiomyocyte cross-sectional area. Data are presented as mean $\pm$ SD ($n = 3$). ^a $P < 0.05$ vs control FVB mice; ^b $P < 0.01$ vs control FVB mice. LV: Left ventricle; RV: Right ventricle.

did not detect significant RV systolic impairment[40]. More recently, Bagheri *et al*[41] used unbiased genetic analyses combined with clinical variables related to pulmonary hypertension and RV function, identifying diabetes as the most statistically significant factor associated with increased pulmonary pressure as measured by echocardiography. Furthermore, a separate clinical study demonstrated that glycosylated hemoglobin, an established marker of long-term glucose control, is an independent predictor of RV global longitudinal strain, suggesting that tighter glycemic management may mitigate RV dysfunction[14].

In general, cardiac dysfunction is predominantly determined by changes in cardiac structures, including the pathological hypertrophy and fibrosis termed structural remodeling, which are mediated by the progressive induction of cardiac oxidative stress and inflammation caused by hyperglycemia (Figure 9)[13]. Cardiac fibrosis plays a key role in the pathophysiological development of DCM. In most animal DCM experiments, increased collagen accumulation can be observed in perivascular loci and/or between myofibers because these changes would impact the myocardial contractility and relaxation[42,43]. The increase in fibrotic-related proteins and mRNA expressions occurred earlier in the LV compared with the RV. The mechanisms that lead to cardiac fibrosis in DCM include activation of the renin angiotensin aldosterone system, inflammatory responses, as well as remodeling of the extracellular matrix mediated by advanced glycation end-product, upregulation of transforming growth factor- β -mediated signaling, and overexpression of CTGF and FN[42,44-46].

Cardiomyocyte hypertrophy collectively results in increased ventricular wall thickness that in turn can contribute to cardiac diastolic and systolic dysfunction. Cardiomyocyte hypertrophy in LV has been shown in OVE26 mice[47]. To our knowledge, the current study is the first to quantify RV hypertrophy in OVE26 mice. The distinct time courses for LV and RV dysfunction and pathophysiological changes in the current study are likely partially influenced by the differences in histological structure and physiological characteristics between the RV and LV. Because pulmonary vascular resistance is much lower than systemic resistance, although the stroke volume of the RV and LV are equal, the cardiac work of RV is much lower than that of LV. In addition, differences in embryological origins, epigenome, transcriptome and metabolome between RV and LV may contribute to the discrepancy in the processes of diabetes-mediated remodeling and cardiac



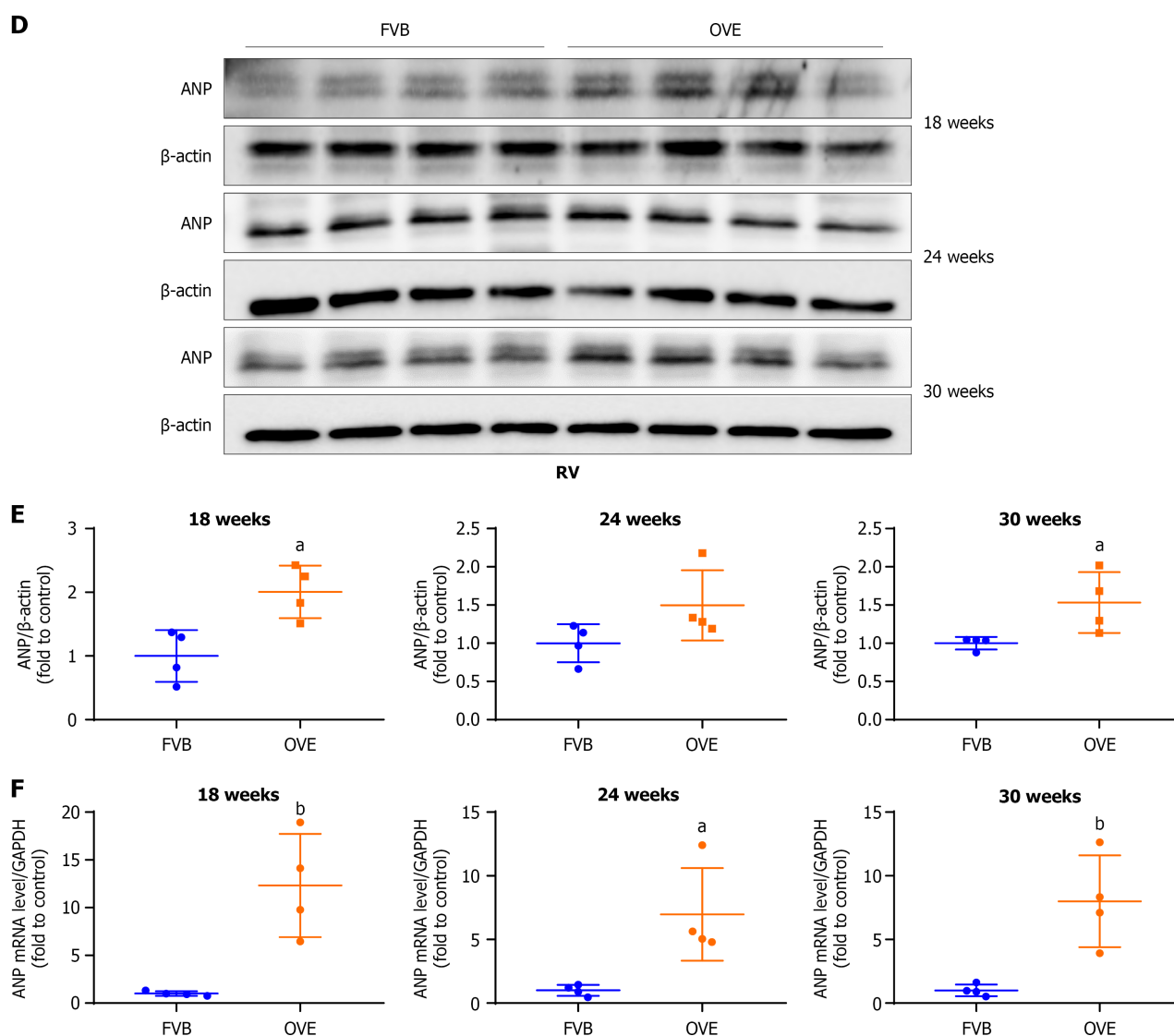


Figure 8 The impact of type 1 diabetes on cardiac hypertrophy in the left and right ventricles of OVE26 and FVB mice. A and B: Changes in atrial natriuretic peptide protein levels in the left ventricle were assayed by Western blot; C: Changes in atrial natriuretic peptide mRNA expression in the left ventricle were measured by quantitative reverse transcription polymerase chain reaction; D and E: Changes in atrial natriuretic peptide protein levels in the right ventricle were assayed by Western blot; F: Changes in atrial natriuretic peptide mRNA expression in the right ventricle were measured by quantitative reverse transcription polymerase chain reaction. Data are presented as mean $\pm$ SD ($n = 4$). ^a $P < 0.05$ vs control FVB mice; ^b $P < 0.01$ vs control FVB mice. LV: Left ventricle; ANP: Atrial natriuretic peptide; RV: Right ventricle.

dysfunction. Based on the present study (Figure 9), we showed a later development of RV dysfunction compared to the LV, suggesting that the LV may play an important role in the development of the RV structure and function in diabetes. This finding is consistent with previous clinical studies. One reported RV dysfunction, commonly accompanied with post-capillary pressure overload, precapillary pulmonary hypertension and LV-RV interaction[34]; another confirmed the decrease in RV global longitudinal strain secondary to LV dysfunction in patients with diabetes[48], although varying conclusions have been noted[14,49]. These mechanisms need to be further explored in the future.

Lung pathology is an additional important target in diabetes[50,51]. Increasing evidence has confirmed the relationship between diabetes and PAH[52]. Subsequently, diabetes-induced PAH generates RV hypertrophy and dysfunction, thereby exacerbating DCM[17]. The damage of vascular pulmonary endothelium produced by inflammation, reactive oxygen species overproduction and upregulation of profibrotic mediators together might contribute to diabetic PAH[53, 54]. Consistent with this paradigm, we showed an increase in RVSP at 30 weeks in OVE26 mice compared to FVB control. In addition, we reported the development of pulmonary pathogenesis in OVE26 mice[55]. Therefore, it is reasonable that RV systolic impairment develops in later stages of DCM in OVE26 mice through the joint effects of direct myocardial injury, diabetic PAH and LV impact on the RV. Therefore, the detailed mechanisms by which T1D induces RV remodeling and dysfunction as well as pulmonary hypertension, remain a critical gap; future research should utilize *in vitro* and *in vivo* studies combined with multi-omics approaches. Whether the features described in the present study are conserved in other T1D and T2D mouse and rat models needs to be further investigated.

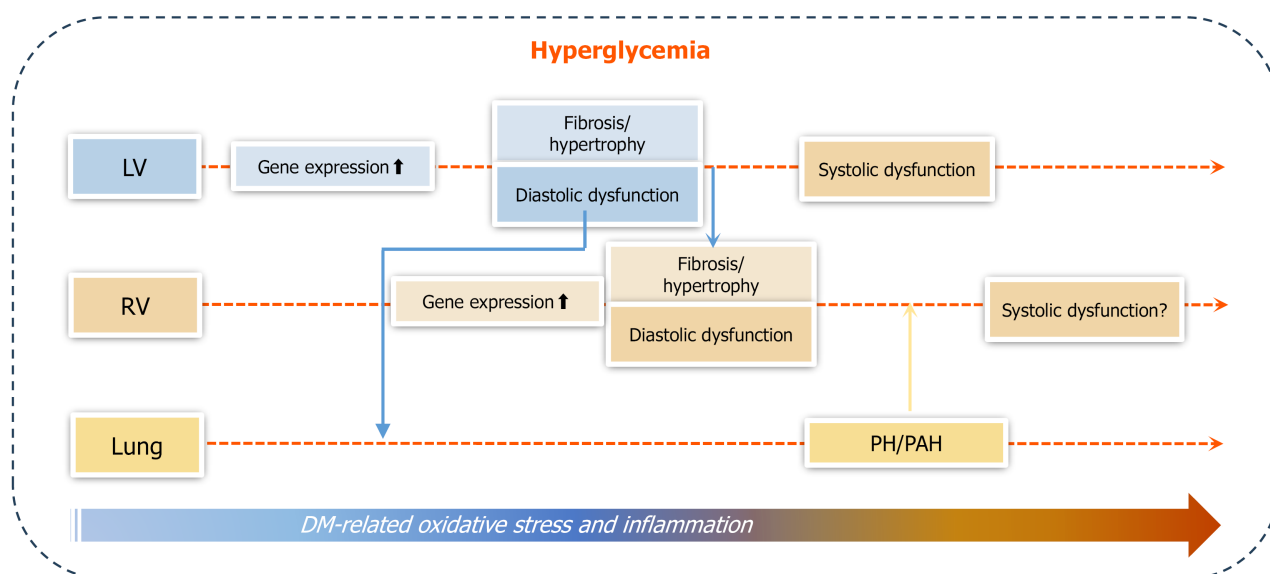


Figure 9 Outline of the main findings of the study. Under hyperglycemic conditions that promote progressive cardiac oxidative stress and inflammation, right ventricular (RV) systolic function remained comparable to controls, whereas left ventricular (LV) systolic function declined in type 1 diabetes (T1D) mice by 30 weeks of age. RV diastolic dysfunction became evident by 18 weeks and worsened by 30 weeks, while LV diastolic dysfunction showed an increasing trend at 12 weeks, reached significance by 18 weeks, and further progressed by 30 weeks. Additionally, RV diastolic dysfunction was accompanied by RV cardiac fibrosis and hypertrophy, which occurred later than the corresponding changes in the LV. Pulmonary arterial hypertension (PAH) developed in T1D mice, evidenced by increased pulmonary acceleration time to pulmonary ejection time ratio and RV peak systolic pressure at 30 weeks. In conclusion, T1D can cause diabetic cardiomyopathy, including both RV and LV dysfunctions, which are mediated by pathological remodeling (hypertrophy and fibrosis) of each ventricle; however, diastolic dysfunction occurs earlier than systolic dysfunction. Mild PAH is present at later stages of T1D, most likely derived from LV dysfunction. The development of PAH may contribute to RV systolic impairment and remodeling. DM: Diabetes mellitus; LV: Left ventricle; RV: Right ventricle; PH: Pulmonary hypertension; PAH: Pulmonary arterial hypertension.

The present research has several limitations: (1) Because the reproductive rate of OVE26 mice was low and their maintenance cost is relatively high, sample size in each group (6-8 mice) was relatively small but consistent with previous studies[56-59]; the RV free wall tissue in the mouse is small (about 15-30 mg), and each RV tissue must be used in histological staining or western blot and PCR; therefore, this resulted in a smaller sample size in each group for some measurements; (2) Longer time-points past 30 weeks were not included in this study. Considering that a 30-week-old mouse is similar to a 20-30-year old human and a 2-week-old mouse is similar to a 1-year old child, we would predict that a 30-week-old mouse and 20-30-year-old human with T1D would have developed cardiac without hyperglycemic control. However, we may consider performing longer-term studies of the OVE26 mice with different levels of hyperglycemic control with insulin or other hypoglycemic medicines; (3) In the present study, we applied the most commonly used Echo variables. Additional cardiac measures may provide additional insights into alterations among RV and LV systolic and diastolic dysfunction; and (4) Although this study has for the first time comparatively investigated the features of dynamic RV dysfunction in a spontaneously developed T1D mouse model, the detail mechanisms by which T1D induces RV remodeling and dysfunction as well as pulmonary hypertension remain to be investigated in other T1D mouse and rat models.

CONCLUSION

In conclusion, this is the first report to our knowledge that compares the onset of RV and LV dysfunction longitudinally in T1D-induced DCM in an animal model. We note that DCM can generate RV diastolic dysfunction in T1D, occurring later than LV dysfunction. Moreover, both RV and LV diastolic dysfunction occur earlier than systolic dysfunction. Mild PAH is exhibited at later stages of T1D and could cause RV systolic impairment and remodeling. These findings may provide novel targets in DCM diagnosis and prognosis evaluation.

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FOOTNOTES

Author contributions: Yu JJ and Xun JX performed experiments, interpreted data, and prepared the manuscript; Han JG, Tan Y, LeBlanc A, Keller BB, Huang J, and Cai L reviewed experimental progression, interpreted experimental data, reviewed and edited manuscripts; Huang J and Cai L designed and oversaw experiments; and they contributed equally to this manuscript and are co-corresponding authors. All authors reviewed and approved the final version.

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