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Effect of valsartan on left ventricular anatomy and systolic function and aortic elasticity

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Abstract

The objective of the study was to examine the effect of a 6-month daily treatment with 160 mg valsartan, an angiotensin II receptor blocker, on the left ventricular systolic function and aortic elasticity of patients with type 2 diabetes mellitus (T2DM) and healthy subjects. This was a prospective, randomized, double-blind, placebo-controlled crossover study. Thirteen healthy control subjects and 11 patients with T2DM were enrolled in the study. Eight control subjects and 4 T2DM patients completed the study. Cardiovascular magnetic resonance was used to evaluate the effect of valsartan on the left ventricular function and aortic elasticity. At baseline, T2DM patients had increased left ventricular mass ($P = .006$) when compared with the healthy controls. In the T2DM patients, treatment with valsartan, in comparison with receiving placebo, resulted in a reduction of aortic radius ($P = .026$) and wall thickness ($P = .032$) of the ascending aorta. In the abdominal aorta, valsartan treatment, when compared with placebo treatment, reduced the arterial compliance ($P = .014$) in the T2DM patients. Valsartan treatment for 6 months decreased the diameter and wall thickness of the ascending aorta in patients with T2DM, but may decrease AC of the abdominal aorta.

1. Introduction

Diabetes is associated with an increased risk for cardiovascular morbidity and mortality that is considered to be related mainly to changes in the lipid profile, accelerated atherosclerosis, endothelial dysfunction, increased platelet aggregability, raised fibrogen levels, and increased plasminogen activator inhibitor–1 activity [1,2]. Diabetes is also associated with a distinct cardiomyopathy, the main clinical feature of which is congestive heart failure in the absence of coronary artery, hypertensive, valvular, congenital, or alcoholic heart disease [3,4]. Diabetic men participating in the Framingham Heart Study had more than twice the risk for development of congestive heart failure compared with nondiabetic participants. The previously mentioned increased risk was shown to be about 5-fold for women [5]. This increased risk implies a direct relationship between diabetes and cardiomyopathy because it persisted despite controlling for other factors that could be related to the development of heart failure such as age, hypertension, coronary artery disease, lipid abnormalities, and obesity. The causes of diabetic cardiomyopathy are not clear, and there is probably a constellation of pathogenic mechanisms leading to myocardial dysfunction [6].

Type 2 diabetes mellitus is associated with impaired vascular elastic properties of the arterial tree, including the large vessels such as the ascending and abdominal aorta [7,8]. Under normal circumstances, the bolus of blood that is propulsed into the arterial system during ventricular ejection creates flow waves that travel distally at a velocity that is largely determined by the elastic properties of the arterial wall and the distal conduit resistances, which induce reflectance waves [9,10]. Reduced elasticity is believed to result in increased systolic pressure and ventricular mass and decreased diastolic coronary perfusion [11].

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Animal studies indicate that treatment with angiotensin II receptor blockers (ARB), in combination with angiotensin-converting enzyme inhibitors or alone, has a beneficial effect on cardiac remodeling and ventricular function after myocardial infarction [12,13]. These beneficial effects are mediated by nitric oxide in heart failure [14]. There is, however, little information regarding humans. In addition, no information is available regarding the effects of angiotensin II blockade in diabetic patients where ventricular dysfunction may exist.

The primary hypothesis of this trial was that indices of left ventricular (LV) function and aortic elasticity are impaired in diabetes, even in the absence of coronary artery disease, and that valsartan, an ARB, may improve LV function and aortic elasticity in the early stages of diabetic cardiomyopathy.

2. Subjects and methods

2.1. Subjects

Twenty healthy nondiabetic subjects and 20 patients with T2DM, aged 21 to 80 years, were recruited. Healthy nondiabetic subjects underwent an oral glucose tolerance test to exclude unknown diabetes. Oral fasting glucose of less than 100 mg/dL and a 2-hour post–oral glucose tolerance test plasma glucose less than 140 were required [15]. Exclusion criteria included clinical coronary artery disease; arrhythmia; heart failure (New York Heart Association class III and IV); stroke or transient ischemic attack; uncontrolled hypertension; macroalbuminuria; severe dyslipidemia (triglycerides >600 mg/dL or cholesterol >350 mg/dL); serious chronic disease that could affect the ability of the subject to participate in the study; treatment with ARBs, glucocorticoids, antineoplastic agents, and bronchodilators; claustrophobia; and subjects unable to have cardiovascular magnetic resonance (CMR) scan (eg, pacemaker, defibrillator).

The protocol was approved by the institutional review board at the Beth Israel Deaconess Medical Center. All participants gave written informed consent. Participants for the study were recruited through local advertisement.

2.2. Methods

This was a prospective, randomized, double-blind, placebo-controlled, crossover study. All participants were evaluated during an initial screening visit and, if suitable, were asked to return and be enrolled in the study. The design of the study is depicted in Fig. 1. The randomization process occurred within groups; and as a result, it was separated for the 2 groups. The first period lasted 6 months, the washout period lasted 2 months, and the second period lasted 6 months. The baseline visit included physical examination, blood tests, and CMR. Participants were randomized at this visit and were started on treatment with either placebo or 160 mg valsartan daily. The second visit, at the end of the first 6-month period, included a physical examination, blood tests, and CMR. The third visit, at the end of the 2-month washout period, included physical examination, blood tests, and CMR. Each participant was switched to the opposite treatment of that of the first period. The exit visit included physical examination, blood tests, and CMR. In all visits, laboratory tests were performed after an overnight fast. Compliance was evaluated by counting the returned tablets.

Plasma glucose, total serum cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, liver function tests, electrolytes, blood urea nitrogen, and creatinine were measured using the Synchron CX analyzer (Beckman/Coulter, Brea, CA). Hemoglobin A_{1c} (HbA_{1c}) (reference range, 4%-6%) was determined in whole blood using ion exchange high-performance liquid chromatography (Tosoh 2.2, Tokyo, Japan).

2.3. CMR measurements

Cardiovascular magnetic resonance imaging was performed on a 1.5-T whole-body scanner (Gyroscan NT/ACS; Philips Medical Systems, Best, the Netherlands), which is equipped with the Powertrack 6000 gradient hardware (23 mT/m, 219-μs rise time), and advanced cardiac software. A 5-element phase array coil was used as the radiofrequency receiver for imaging of the heart and thoracic aorta, and the body coil was used for imaging of the abdominal aorta.

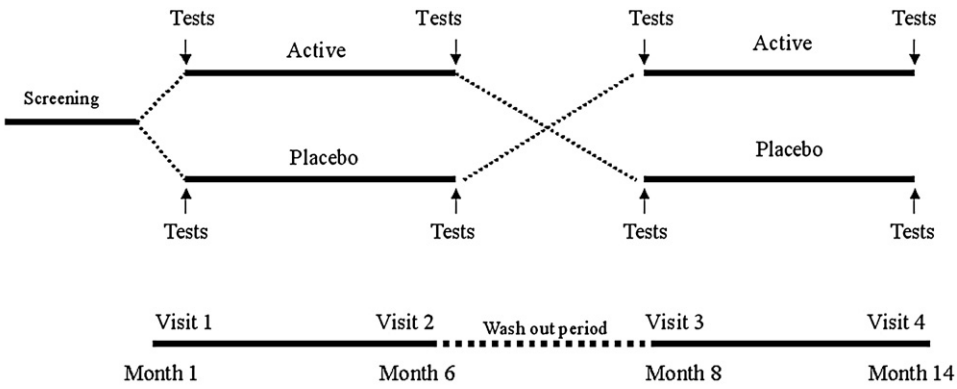

Fig. 1. Scheme of the clinical trial.

After initial localizing "scout" images, cine LV long-axis (2-chamber), 4-chamber, and contiguous short-axis images were obtained using a steady-state free processor breath-hold cine sequence. Temporal resolution of the images was 30 to 35 milliseconds, and the duration of the breath-hold was 10 to 12 seconds (depending on the heart rate). Oblique transverse images were obtained perpendicular to the long axis of the aorta at the sinotubular junction (ascending aorta) and immediately proximal (cephalad) to the renal arteries (abdominal aorta). Imaging was performed using a retrospective electrocardiographic-gated phase-encoded gradient-echo sequence with the following parameters: field of view, 210 × 300 mm; matrix, 96 × 128; echo time = 6.5 milliseconds; repetition time = 15 milliseconds; flip angle, 30°; slice thickness, 6 mm; and velocity encoding, 300 cm/s. Finally, to determine aortic wall thickness, a high-resolution black blood image was obtained at both the ascending thoracic and abdominal aorta using a turbo spin-echo (TSE) sequence with a dual inversion pulse with the following parameters: field of view, 320 × 400 mm; matrix, 336 × 512; echo time = 20 milliseconds; repetition time equal to the RR interval in milliseconds; TSE factor=12; flip angle, 90°; and slice thickness, 6 mm. The latter scan was performed during breath-holding to minimize respiratory artifacts (breath-hold duration of 10-12 seconds). For the phase-encoded images, respiratory motion compensation was accomplished by measuring multiple signal averages (NSA = 4).

During the examination, blood pressure was noninvasively measured using an automated sphygmomanometer (Dinamap; GE Medical Systems, Madison, WI), with the cuff placed at the calf. The mean of 3 values was used for calculations of vascular elasticity.

Image data were transferred off-line to a ViewForum workstation (Philips Medical Systems) for further analysis. Left and right ventricular endocardial and epicardial contours for all short-axis end-diastolic and end-systolic images were manually traced. Using the commercially available analysis package, volumetric assessment of mass, end-diastolic and end-systolic volumes, ejection fraction (EF), stroke volume, and cardiac output were derived for the left and the right ventricles.

Aortic maximal and minimal cross-sectional areas were determined from the phase-encoded flow scans using semiautomated ViewForum software. Thus, the phases with the maximal and minimal aortic diameter/area were determined and used in the calculations for aortic elasticity. For assessment of the aortic wall thickness, 2 measurements were obtained in areas free of artifact; and the mean of the 2 values was calculated.

Vascular elasticity was described with the following parameters:

Arterial compliance (AC): defined as the absolute volume increase within an arterial segment during the cardiac cycle divided by the arterial pulse pressure. The AC per unit length (1 mm) is AC = $\pi[D(s)^2 - D(d)^2]/\{4[P(s) - P(d)]\}$, where $D(s)$ and $D(d)$ are the systolic and diastolic diameters of the artery and $P(s)$ and $P(d)$ are the systolic and diastolic blood pressures, respectively. Arterial compliance is measured in square millimeters per kilopascal (1 kPa=7.6 mm Hg).

Stiffness index (SI): defined as the natural logarithm of the ratio of systolic to diastolic blood pressure divided by the circumferential arterial strain (CAS), which is the fractional increase in arterial diameter during the cardiac cycle. Thus, SI is a unitless quantity and considered to be relatively independent of blood pressure. SI = $\ln[P(s)/P(d)]/CAS$, where CAS = $[D(s) - D(d)]/D(d)$.

Pressure-strain elastic modulus (Ep): defined as the arterial pulse pressure divided by the CAS: Ep = $[P(s) - P(d)]/CAS$ and is measured in kilopascals.

Young elastic modulus (YEM): defined as the ratio of stress (force per unit area) to strain and measures arterial stiffness controlling for vessel wall thickness. YEM = $(R/WT)\{[P(s) - P(d)]/CAS\}$, where R is the outer arterial radius and WT is the wall thickness (intima plus media). The YEM is measured in kilopascals.

2.4. Data analysis

The Minitab statistical package (Minitab, State College, PA) was used for the statistical analysis. The analysis for the effect of valsartan treatment was performed using a parametric test (ie, paired t test) for normally distributed data and a nonparametric test (ie, Wilcoxon matched-pair signed rank test) for data that are not distributed normally to compare the changes during the placebo and active period treatments in each group. The t test was used to compare the baseline characteristics between the healthy nondiabetic subjects and the T2DM patients for normally distributed data and the Mann-Whitney for nonparametric data. The results are presented as mean ± SD for normally distributed data and median (25-75 percentile) for data that are not distributed normally. Single and multiple regression analysis was also performed. Statistical significance was accepted at the 95% confidence level ($P < .05$).

3. Results

3.1. Comparisons in CMR measurements between healthy subjects and T2DM patients at baseline

Thirteen healthy control subjects and 11 patients with T2DM were enrolled. The baseline demographics of those who completed the study in each group are shown in Table 1. Type 2 diabetes mellitus patients had higher body mass index (BMI) ($P = .002$), systolic blood pressure ($P = .03$), fasting blood glucose ($P = .0001$), and HbA_{1c} ($P = .0001$). Baseline CMR data are shown in Table 2. The T2DM patients had higher LV mass ($P = .006$). When all subjects were considered as 1 group, significant correlations were found between LV mass and HbA_{1c} ($r = 0.58$, $P = .005$), fasting

Table 1
Clinical characteristics of participants

	Healthy control subjects	T2DM	P
n	13	11	
Age, y	51 ± 13	55 ± 11	NS
Male (%)	8 (62%)	5 (45%)	NS
DM duration, y	–	5 ± 3	
BMI	26.5 ± 5.9	35.9 ± 7.4	.002
Systolic BP (mm Hg)	123 ± 21	142 ± 19	.03
Diastolic BP (mm Hg)	71 ± 12	78 ± 10	NS
Fasting glucose (mg/dL)	74 ± 9	126 ± 40	.0001
HbA_{1c}	5.2 ± 0.4	7.5 ± 1.4	.0001
Total cholesterol (mg/dL)	187 ± 50	179 ± 46	NS
LDL (mg/dL)	98 ± 41	84 ± 55	NS
HDL (mg/dL)	62 ± 26	48 ± 13	NS
Triglycerides (mg/dL)	134 ± 76	195 ± 169	NS
BUN	16 ± 5	16 ± 5	NS
Creatinine	0.8 ± 0.2	0.7 ± 0.2	NS
Urine albumin-creatinine ratio	11 (3:64)	–	
Antihypertensive treatment			
β-Blockers	0	0	
Diuretic	0	1	
Calcium antagonists	0	2	
ACE inhibitors	0	5	
Diabetes treatment	0		
Diet only		1	
Oral agents			
Metformin		6	
Sulfonylureas		5	
Pioglitazone/rosiglitazone		0	
Insulin		2	
Statins	0	4	
Aspirin	1	2	

Mean ± SD or median (25:75 percentile). BP indicates blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BUN, blood urea nitrogen; ACE, angiotensin-converting enzyme; NS, not significant.

blood glucose ($r = 0.53$, $P = .008$), and BMI ($r = 0.64$, $P = .001$); but in multiple regression analysis, only BMI retained statistical significance. There were no differences in any of the aortic parameters.

3.2. Effects of valsartan treatment on CMR measurements in T2DM patients and the healthy control subjects

Eight control subjects and 4 T2DM patients completed the study. Five subjects were lost to follow-up, 6 subjects withdrew consent because they were unable to comply with the study protocol, and 1 subject withdrew because of mild dizziness that resolved after stopping the study medication. There were no differences between those who completed the study and those who failed to complete the study in any of the clinical characteristics that are listed in Table 1.

Treatment with valsartan did not have any effect on systolic and diastolic blood pressure, fasting blood glucose levels, and HbA_{1c} in both groups. The comparison between difference in the CMR measurements during the valsartan and placebo period treatment is shown in Table 3. There were no differences in all performed cardiac measurements between changes observed during the valsartan and placebo treatment periods in both the healthy control subjects and the T2DM patients. In the ascending aorta measurements of T2DM patients who completed the study, treatment with valsartan, in comparison with receiving placebo, resulted in a reduction of aortic radius ($P = .026$) and wall thickness ($P = .032$). In the abdominal aorta, valsartan treatment, when compared with placebo treatment, reduced the AC ($P = .014$) in the T2DM patients.

4. Discussion

The main finding of this study is that administration of 160 mg of valsartan, an ARB, for 6 months decreased the radius and wall thickness of the ascending aorta in T2DM patients, whereas it had no measurable effects in healthy control subjects. In the abdominal aorta, valsartan decreased the AC in the T2DM patients, but had no effect in the controls.

Previous studies have suggested that the development of cardiomyopathy starts early in the course of diabetes and that diabetic patients without any clinical findings suggestive of heart failure may have significant abnormalities of both systolic and diastolic function [16-19]. In the present study, we included T2DM patients with no clinical cardiovascular

Table 2
Baseline MRI cardiac measurements

	Healthy control subjects	T2DM	P
Cardiac measurements			
Systolic BP (mm Hg)	136 ± 31	153 ± 27	NS
Diastolic BP (mm Hg)	40 ± 10	45 ± 13	NS
Heart rate (beat/min)	71 ± 5	71 ± 5	NS
LV EDV (mL)	136 ± 31	153 ± 27	NS
LV ESV (mL)	40 ± 10	45 ± 13	NS
EF	71 ± 5	71 ± 5	NS
LV mass (g)	98 ± 23	133 ± 33	.006
Forward aortic flow	80 ± 26	88 ± 15	NS
MR fraction	18 (9:25)	11 (2:18)	NS
Ascending aorta measurements			
Aortic radius	15.1 ± 1.7	15.1 ± 1.8	NS
Wall thickness (mm)	2.06 ± 0.19	2.16 ± 0.14	.069
Compliance (AC; mm^2/[kPa mm])	0.14 (0.10:0.30)	0.13 (0.09:0.23)	NS
SI	7.18 ± 4.23	8.66 ± 5.13	NS
Ep (kPa)	84 ± 52	125 ± 70	NS
YEM (kPa)	613 ± 374	881 ± 491	NS
Abdominal aorta measurements			
Aortic radius	9.2 ± 1.0	9.8 ± 1.3	NS
Wall thickness (mm)	1.76 ± 0.19	1.81 ± 0.20	NS
Compliance (AC; mm^2/[kPa mm])	0.064 (0.007:0.14)	0.043 (0.006:0.099)	NS
SI	4.24 ± 2.3	5. 0 ± 2.9	NS
Ep (kPa)	49 ± 27	72 ± 36	NS
YEM (kPa)	270 ± 158	412 ± 173	.056

Data are presented as mean ± SD or median (25:75 percentiles). EDV indicates end-diastolic volume; ESV, end-systolic volume; MR, mitral regurgitant.

Table 3
Changes with the valsartan treatment when compared with changes during placebo treatment period in the healthy controls and the T2DM patients

	Healthy control subjects	*P*	T2DM	*P*
Systolic BP (mm Hg)	0 (−15:15)	NS	8 (−38:54)	NS
Diastolic BP (mm Hg)	1 (−9:10)	NS	−5 (−23.91:14.41)	NS
Heart rate (beat/min)	2 (19:22)	NS	6 (−11:23)	NS
LV EDV (mL)	−26.6 (−90.5:37.4)	NS	−1.75 (−14.24:10.74)	NS
LV ESV (mL)	11.86 (−11.49:35.21)	NS	3.25 (−6.68:13.18)	NS
EF	−4.29 (−18.27:9.70)	NS	−2.25 (−11.65:7.15)	NS
LV mass (g)	−2.3 (−27.7:23.2)	NS	−3.3 (−47.3:40.8)	NS
Forward aortic flow	−17.6 (−69.2:34.0)	NS	−5.50 (−20.73:9.73)	NS
MR fraction	−8.7 (−36.7:19.4)	NS	2.81 (−27.35:32.96)	NS
Ascending aorta				
Aortic radius	−0.160 (−1.068:0.748)	NS	−0.494 (−0.878:−0.110)	.026
Wall thickness (mm)	−0.0786 (−0.2816:0.1245)	NS	−0.2750 (−0.5047:−0.0453)	.032
Compliance (AC; mm^2/[kPa mm])	−0.538 (−1.790:0.713)	NS	−0.0588 (−0.1779:0.0603)	NS
SI	0.12 (−7.19:7.44)	NS	5.08 (−12.08:22.24)	NS
Ep (kPa)	−6.5 (−126.7:113.8)	NS	44.4 (−195.2:284.0)	NS
YEM (kPa)	79 (−869:1026)	NS	361 (−1143:1865)	NS
Abdominal aorta				
Aortic radius	−0.613 (−1.564:0.338)	NS	−0.078 (−1.069:1.225)	NS
Wall thickness (mm)	0.129 (−0.232:0.490)	NS	0.400 (−0.128:0.928)	NS
Compliance (AC; mm^2/[kPa mm])	−0.515 (−1.694:0.664)	NS	−0.0639 (−0.1036:−0.0242)	.014
SI	−0.178 (−2.37:2.01)	NS	3.09 (−2.11:8.29)	NS
Ep (kPa)	−3.3 (−33.9:27.4)	NS	34.4 (−43.1:111.9)	NS
YEM (kPa)	−40 (−265:184)	NS	89 (−234:412)	NS

Data are presented as mean and 95% confidence intervals.

disease and a relatively short duration of diabetes (mean, 5 ± 3 years); but our results are in agreement with the previous studies because we found that the diabetic patients had increased wall thickness and LV mass when compared with the controls.

There are very limited data regarding the effect of ARBs on cardiac function in diabetes. A recent study that included diabetic patients without hypertension or heart disease who were treated for 6 months with candesartan, another ARB, showed an improvement in diastolic dysfunction and attenuation of myocardial fibrosis, suggesting that ARBs may regulate collagen turnover by facilitating collagen degradation [20]. Previous studies in our unit have shown that valsartan treatment for 3 months, at the same dose as in the present study, results in considerable improvement of blood flow in the skin microcirculation of diabetic patients but had no effect in the skin microcirculation of healthy control subjects [21]. Furthermore, the same studies indicated that valsartan exerts its beneficial effects by reducing the activity of poly (adenosine diphosphate-ribose) polymerase, which is increased in diabetes and is associated with endothelial dysfunction [22,23].

The most interesting finding of the present study was the effect of valsartan on the elasticity of the ascending aorta. In the T2DM patients, valsartan reduced the vessel radius and wall thickness of the ascending aorta. As the above measurements are correlates of subclinical atherosclerosis, this finding, if confirmed at a larger cohort, may be very important because it indicates a possible beneficial pleiotropic effect of valsartan on atherosclerosis, potentially independent of reduction of the peripheral blood pressure [24].

An unexpected finding was the decrease of *AC*, which is defined as the absolute volume increase within an arterial segment during the cardiac cycle divided by the arterial pulse pressure, in the abdominal aorta of the valsartan-treated T2DM patients. The calculation of compliance is based on the measurement of both the systolic and diastolic aortic diameter and blood pressure. Although CMR can accurately measure changes in the aortic diameter during valsartan treatment, previous studies have indicated that changes in the central blood pressure are not reflected by changes in the peripheral blood pressure measurements; and this may be the main reason for the obtained results [25]. Furthermore, all other indices of vascular elasticity were not affected; and there are no pathophysiologic mechanisms that would explain such deterioration in vascular compliance. As a result, we believe that the physiologic significance of this finding is doubtful. Nevertheless, this finding deserves further investigation in a larger sample of patients and possibly during longer periods of treatment.

In the present study, we have used CMR for evaluating the effect of valsartan on LV function and aortic elasticity. The main reason for this is that this technique is currently

considered as the "criterion standard" for measurement of LV mass and volumes [26,27]. Because of extremely high accuracy and reproducibility, CMR allows for high statistical power to detect small differences in cardiac structure and function between study groups, with even a small sample size. Accordingly, for clinical trials, CMR compares favorably to echocardiography and is becoming the dominant imaging modality in cardiovascular clinical research [28-30]. Cardiovascular magnetic resonance can also most accurately measure small changes in the aortic lumen cross-sectional area with very high temporal resolution and can quantify blood flow through large vessels. Therefore, CMR is uniquely suited for the evaluation of the elastic properties of large arteries [10,31-33].

The current study has its limitations, of which the most prominent is the considerable number of subjects who did not complete the study (9; 37% of the participants). We believe that the main reason for this was the long duration of the study and the crossover design. This, combined with the small number of subjects that were recruited, resulted in a rather small study cohort. However, the fact that valsartan was found to improve certain indexes of ascending aortic function in T2DM patients but not in controls indicates that, despite these limitations, the study has accomplished its primary scope, which was to provide proof of concept and justify the conduction of additional studies in the future. As the conduction of such studies is cumbersome and carries a heavy cost, we believe that the initial conduction of a small study that aims primarily to provide proof of concept is fully justified and that the current study has achieved its main goals.

In summary, our results indicate that valsartan treatment for 6 months decreased the diameter and wall thickness of the ascending aorta in T2DM patients but may decrease AC of the abdominal aorta.

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