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A Novel Hypothetical Method to increase the Dimensions of the Coronary Arteries when Required

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Abstract

Background: The purpose was to develop a novel hypothetical method to increase the size of coronary arteries.

Methods: In the long-term observation the coronary sizes were dilated in three unexpected scenarios. The coronary artery sizes were observed in patients with mitral stenosis (n=59) by angiogram prior to percutaneous balloon mitral valvuloplasty or valve replacement surgery for severe mitral stenosis. The coronaries of patients with patent ductus arteriosus who underwent surgical closure in the past (n=12) were examined by echocardiogram. Patients with renal failure on long-term dialysis through peripheral arterio-venous fistula without left ventricular hypertrophy (n=17) were studied by echocardiography. Normal age, weight and sex matched coronary sizes served as controls in the study. All these observations were made over a period of 11.5 years.

Results: The sizes of coronaries in patients with mitral stenosis, patients who underwent closure for patent ductus arteriosus, and in patients on hemodialysis through arteriovenous fistulas were higher than normal controls ($p<0.05$, for all). A hypothetical model to increase the coronary sizes could be developed based on the analysis of the differential equations of Poiseuille's. The proposed method is creating a peripheral arterio-venous fistula, which could be closed later electively by a percutaneous method/surgery. The closure time needs to be determined by experimental studies. The other methods could be a continuous exercise program or usage of beta-blockers.

Conclusion: A novel hypothetical method of peripheral arteriovenous fistula formation could potentially increase the size of the coronaries, and this could be closed later.

Keywords
Coronary dimensions; Poiseuille's Equation; Arteriovenous fistula; Coronary dilatation; Wall shear stress; Coronary blood flow; Atherosclerosis; Angiogenesis

Introduction

It is a common observation to visualize thin coronaries in long-standing diabetic and hyperlipidemic individuals. In patients with refractory angina, the symptoms persist even after optimal coronary artery revascularization by medications, stents or coronary artery bypass grafts[1,2]. Approximately 60,000 cases are added every year in this category in Europe or the US[1]. It is interesting to identify a method to increase the size of the coronary arteries. This would be challenging and therapeutically useful. An increase in size would result in the lesser incidence of coronary events. Especially in diabetic patients, there is a reduction in arterial sizes due to deposition of advanced glycosylated end products[3]. Hyperlipidemic conditions due to deposition of the micro cholesterol particles also lead to a reduction in the coronary dimensions and result in increased coronary events[4]. Reduction in the caliber of the blood vessels leads to a reduced volume of blood flow as well as an increase in wall shear stress[5] and results in earlier coronary events.

The primary objective of the study was to identify a novel possible method which could increase the dimensions of the coronaries. Though coronary dilatation cannot prevent atherosclerosis directly, it is possible to reduce atherosclerotic processes by reducing wall shear stress, which initiates endothelial dysfunction. In this study, after a series of observations in various unexpected clinical scenarios a theoretical model has been proposed as a derivative of physical equations governing the fluid dynamics.

Methods and Results

The study was developed after an observation of a series of cases in different clinical settings in which coronary arteries were dilated. Three clinical conditions were identified and studied, in which the coronary arteries were widened, and the left ventricles had the normal dimensions. In these three clinical conditions the increase in coronary sizes was unexpected. Conditions which are known to increase or decrease the coronary and left ventricular dimensions were excluded. After observations in the initial three years, a prospective case-controlled study was planned. The primary outcome of the study was to identify dilated coronaries in patients with normal left ventricular dimensions, compared to the controls. The recruitment of the patients was on a continuous non-randomized method. This is due to a limited number of patients available for the study. The study was not blinded, and the author was aware of the subjects as well as the controls. The observations were made over a period of 11.5 years. Coronary diameters were measured in the left main coronary artery (LMCA), Left anterior descending artery and the right coronary artery within 3mm from the coronary ostium (Philips IE33, HP Sonos 5500 and Sonosite M-Turbo).

Rheumatic Mitral Stenosis

Observations in the coronary angiograms (n=23) (Siemens Axiom Artis) before mitral balloon valvuloplasty (figure 1) or as a preoperative workup (n=12) for a mitral valve replacement for severe calcific mitral stenosis (figure 2) showed a mild increase in the coronary sizes instead of the expected small caliber since the left ventricle is usually small in this condition compared to the controls (figure 3). During this period balloon mitral valvuloplasty was performed in 148 patients. However, a coronary angiogram was performed in only 23 patients. The mean age of the patients was 37±7 yrs. (median 38, range 23 to 52 years).

In a further subset of 24 patients out of the 148 patients who underwent balloon mitral valvuloplasty, left ventricular angiograms were performed in the initial period before the year 2011 (Figure 4). The patient profile was similar to those patients who underwent balloon mitral valvuloplasty subsequently after year 2010. In these patients, direct coronary angiogram was not performed, and it was a protocol to perform left ventricular (LV) angiogram at that time to look for the mitral valve calcification and to quantify the extent of mitral regurgitation. Diagnostic coronary angiogram as a routine was performed only in patients more than fort-five years, which is a standard guideline. These patients LV angiograms were reviewed and the mean LMCA 4.3±0.3mm and LAD 3.5±0.2mm dimensions were significantly higher than the normal controls. Also, none of these patients had coronary artery disease.

The mean age of patients who underwent surgery (mitral valve replacement) for isolated severe mitral stenosis was 43±6 yrs. (n=12). (median 45; range 28 to 57). Patients with other valvular lesions and mitral regurgitation were excluded. All these patients underwent angiogram before the surgical procedure (supplement figures 6 and 7). All the patients successfully recovered after surgery. Patients with any hyperdynamic circulation states like anemia, pregnancy or thyrotoxicosis, and patients with hypertension or the presence of left ventricular hypertrophy were excluded.

Creatinine levels were normal except in 1 patient where the creatinine was 1.4 mg/dl, and the coronaries were not dilated in this patient. The mean left main coronary artery (LMCA) diameter 4.2±0.2mm was, and the mean proximal right coronary artery (RCA) 3.2±0.3mm diameter and proximal LAD 3.45±0.2mm diameters and the proximal left circumflex artery (LCA) were 3.3±0.3 mm. None of these patients had coronary artery disease (figures 1 and 2, and supplement figures 1 to 7).

The control patients (n=32) were patients with normal chamber dimensions and normal coronaries who underwent angiogram for evaluation of chest pain after a stress test. The control patients were age-sex-weight matched without other co-morbidities or valvular disorders, and they were selected retrospectively in a randomized non-blinded fashion. The control (figure 3 and supplement figures 8 to 12) values of the normal coronary artery sizes in a similar age and body size-matched controls for LMCA was 3.4±0.3mm, proximal LAD was 2.9±0.3mm, the proximal RCA was 2.7±0.3mm, and the proximal LCA - 2.8±0.2mm. The values were significant by t-test ($p<0.05$, for each).

Baseline characteristics are given in the table 1. Out of the total 59 patients in this category, 51 had dilated coronaries compared to control, four had only mildly dilated vessels, three had normal sized vessels; one patient had a smaller vessel and this patient had higher creatinine value of 1.4mg/dl.

Patent Ductus Arteriosus

Patent ductus arteriosus is a congenital vascular connection between the aorta and pulmonary artery. Patients (n= 12) with large shunts who underwent surgery in the past were analyzed for the coronary sizes by echocardiography. Baseline characteristics of this patient group is given in table 2. It was observed that the coronary arterial sizes were larger than the usual, which was observed by echocardiography analysis. The size of the aorta in these patients was normal. In all these cases surgical/coil closure was performed at least four years before the echocardiography these observations of

coronary dilatations (figure 5, upper panel). The mean age of the patients was 17±7 yrs. None of the patients had hyperdynamic circulations like anemia, thyrotoxicosis or peripheral arteriovenous fistula. The mean LMCA diameter was 4.25±0.4mm, LAD was 3.6±0.3, and the mean RCA diameter was 3.4±0.2mm.

The control patients (n=12) were normal age-sex-weight matched patients without other co-morbidities. They had normal chambers and coronary dimensions and they were selection was made in a randomized method. The control values of normal LMCA, LAD and RCA measured by the similar technique was 3.4±0.4mm, 3.0±0.3mm and 2.8±0.3mm respectively (Figure 5 upper panel, and 6). The values were statistically significant ($p<0.05$, for each). The RCA was co-dominant or dominant in all these cases. Visual assessment (eyeballing) of the coronary arteries showed a significant increase in the size of the coronary vessels in these patients compared to the similar age and body-size matched controls (figure 7). All echocardiographic measurements of the coronary arteries were performed with the same magnifications. Also, in all the cases except one, the coronary arteries were dilated compared to the controls giving a high statistical power.

Patients on hemodialysis through the peripheral arterio-venous (AV) fistula

Patients who undergo dialysis (n=17) with peripheral arteriovenous fistula were analyzed for their coronary sizes. Patients who already have left ventricular hypertrophy/dilatation were excluded, as a left ventricular hypertrophy/dilatation could increase the size of the coronary vessels to overcome the demand-supply mismatch in coronary blood flow. The control patients (n=17) were normal healthy age, sex and weight matched controls without other comorbidities.

The coronary dimensions of the patients with A-V fistula showed larger dimensions. These observations in the coronary arteries were made by echocardiographic evaluation (figure 5 lower panel and figure 8). The mean age of the patients was 54±9 yrs. (median 53; range 41,65). Other baseline characteristics of the patients are given in table 3. The mean LMCA diameter was 4.0±0.3mm, LAD was 3.6±0.2mm, and the mean proximal RCA diameter was 3.3±0.3mm; in the control patients the LMCA diameter was 3.4±0.3mm, LAD 3.2±0.2mm and RCA was 2.8±0.4mm. The values were statistically significant ($p<0.05$ for all). The RCA was co-dominant or dominant in all these cases. Visual assessment (i.e., eyeballing) of the coronary arteries showed a distinct increase in size of the coronary vessels. All echocardiographic measurements of the coronary arteries were performed with the same magnifications. In 16 out of the 17 cases, the coronary dimensions were elevated in varying degrees, and in one patient the coronary dimensions were not increased.

Statistical power calculation

Retrospective power calculations were performed based on the observed standard deviations in each category and a minimum significant increase (minimum difference) in arterial dimensions by 0.5mm. A minimum in each group to be studied based on the standard deviation was about ten patients. Hence, the study has the minimum required power to prove the concept, though this is not a categorical number. Based on the analysis, the study results are deemed useful [6].

Discussion

The results presented in the study are from 3 subsets of dis-jointed patient subgroups, who are not related to each other, and the study was performed in various timings. They had one aspect in common, which was the varying degrees of dilatation of coronaries, without dilatation or hypertrophy of the left ventricle. In mitral stenosis, this could be due the fall in the mean arterial pressure compared to the controls, and in other two subgroups, it is possibly related to the existing or the closed arterio-ventricular fistulas. This could be due changes in physical mechanics or cellular signaling. Hyperdynamic circulation as the only mechanism for coronary dilatation in A-V fistula patients is not possible, as these patients had normal chamber dimensions.

Application of Poisueille's equation

Poisueille's law states that the velocity of the steady flow of a fluid through a narrow tube varies directly as the pressure and the fourth power of the radius of the tube and inversely as the length of the tube and the coefficient of viscosity. In these three conditions in the study, the diastolic or the coronary perfusion pressure tends to be low, and the biological response is to dilate the vessels. The study shows some interesting observations on the dilated coronary arteries in specific scenarios. The controls were normal patients, and when compared to diabetic vessels these coronary dimensions would be much higher. Analyzing the Poisueille's equation a reduction in blood pressure especially in the diastolic blood pressures would increase the radius of the blood vessels in the long term[7]. The coronary arteries are usually larger than the normal in patients with aortic regurgitation where the diastolic pressures are low. However, in this condition, the aorta is often dilated and left ventricular hypertrophy is seen. Even in other states like rheumatic mitral regurgitation the coronary arteries are dilated. However, they are often associated with left ventricular dilatation with or without hypertrophy.

The aorta and left ventricles are of standard caliber in all the three study groups. Also, in chronic renal failure on dialysis, the left ventricle is often dilated with hypertrophy. The patients chosen in this study with chronic renal failure did not have either dilatation or hypertrophy of left ventricle.

A lowering of blood pressure, could orchestrate a series of translational pathways, and result in the dilatation of the coronaries. The coronary blood flow and pressures are reduced in mitral stenosis, which improves with percutaneous balloon mitral valvuloplasty [8,9]. In patients with mitral stenosis, there is hypertrophy of the right ventricle. Hence, the right coronary or the circumflex artery would tend to be larger. However, the interesting observation is that the left anterior descending artery was also dilated in-spite of the smaller left ventricle usually seen in this condition.

Cellular mechanisms

Baroreceptors are located in the coronaries, which are similar to the baroreceptors of the aorta[10]. These baroreceptors could mediate the changes through various signaling pathways. Possibly these mediators could be vascular endothelial growth factors[11], hepatocyte growth factors [12,13] and non-canonical WNT pathways[14-17] or Mastermind proteins [18] through NOTCH signaling [19]; Hedgehog pathways[20]. Further investigations are required to identify the exact mechanism of these observations.

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Growth factors like vascular endothelial growth factors and hepatocyte growth factors are known to have a significant role in the signaling of vessel growth. There is also an interesting observation that by creating an arterio-venous fistula the progression of chronic renal failure to end-stage renal failure is delayed [21].

Hence, the formation of the arterio-venous fistula may increase in size of the coronary arteries. This could have clinical therapeutic benefits, which would be reflected by a lower incidence in coronary events. It has been observed in various studies that enhanced external counter pulsations can reduce angina in patients with refractory angina [22, 23]. The observations in this study possibly explain the variations in blood pressures induced by enhanced counter pulsations could be the mechanism for better clinical performance in these patients [24].

There is also a potential disadvantage of the formation of an arteriovenous fistula like tachycardia, which could be managed with medications. However, as observed in this study in patients with patent ductus arteriosus who underwent closure in the past the beneficial effects of an increase in the size of the coronary vessels persist for many years even after the closure of the patent ductus arteriosus. Hence, the peripheral arteriovenous fistula, which when created, could be closed later by either surgical or percutaneous methods. To reduce the complications induced by the arteriovenous fistula, the connections could be performed in distal locations, for example, in the radial/ ulnar artery instead of the proximal brachial artery.

Limitations

The number of patients in each category is not very large. The incidence of normal echocardiographic findings in patients on chronic hemodialysis is rare, and also the number of patients turning for follow-up being asymptomatic few years after patent ductus arteriosus closure is also not common. Moreover, nowadays, due to early treatment by balloon mitral valvuloplasty, the number of patients treated with valve replacement for mitral stenosis is rare. Hence, the principle was to recruit as large patient numbers as possible. Angiogram during balloon mitral valvuloplasty was performed only after some initial observations of coronary dilatations. Also, in 24 cases undergoing balloon mitral valvuloplasty before 2011, the measurements of the coronaries were based on left ventricular angiogram pictures, which are not very accurate. Nevertheless, the observation was convincing, as the coronaries are dilated.

In some conditions in the study, coronary sizes were measured by echocardiography as in patients with closed patent ductus arteriosus, and in patients with renal failure on hemodialysis, which is not the gold standard to evaluate the coronary sizes. A high degree of intra and inter-observer variability was noticed for the coronary size measurements[25]. Especially when the coronary sizes are less than 3mm. However, anatomical assessment is feasible and in children with Kawasaki's disease[26], the coronary size measurement is performed with echocardiography in many centers routinely including our institution[27]. In this study the dilated coronaries were more than 3mm. Due to ethical considerations angiography was not contemplated in these patients. Nevertheless, this is a rare and specific group of patients selected in the study, and by visual assessment the observations were outstanding.

Right heart strain

The concept of volume overload and right atrial and ventricular dilatation and RV strain and dysfunction which is progressive over time is well known [28,29]. These studies have a median follow up period of about 3.9 (IQR 2.4-6.4) years, and the incidence of RV dysfunction is about 35% [30]. The RV dysfunction is more seen in patients with brachio-cephalic fistulas than in the radial venous fistulas[29]. Hence, if a peripheral arteriovenous fistula is formed for this purpose the closure time could be in the range of 1.5 to 2 years to prevent complications.

Future perspective

The concept outlined in the study is hypothetical and further validation accurately is only possible after an animal study by creating an arteriovenous fistula, and studying the angiogram before and after the A-V fistula possibly with a long-time interval of about 6m to 1 year in large animals. Echocardiographic measurement of coronary arteries before and after the arteriovenous fistula in clinical practice can be performed, however, this method is less accurate to conclude. The effect of beta-blockers, which reduce the heart rate and blood pressure, and its impact on coronary anatomical variations need to be studied. Also, the effect of a continuous exercise program modifying the coronary sizes needs to be determined.

Conclusion

There is a possibility for a novel therapeutic method of AV fistula formation as a method to increase coronary sizes. This concept needs to be evaluated by experimental studies in animals by observing coronary dimensions before and after creating an arteriovenous fistula.

Author contributions

MCA conceived the idea and method, designed the study, performed the procedures and echocardiography, and wrote the paper.

Disclosures: None

Competing Interests: None

Source of funding: None

Ethical considerations: Informed consent for the procedures was taken, and institutional ethical review board approved the study (pims/13012011/C1/G).

Table 1. Baseline characteristics of patients undergoing balloon mitral valvuloplasty/surgery.

Parameters	Values, n=59($23^{BMV>2010}$+$24^{BMV<2011}$+$12^{Surgery}$)
Age, yrs.	39±8
Sex, M/F	14/31
Diabetes, n	1
Hypertension, n	1
MV area Pre-procedure, cm^2	0.9 ± .1
MV area Post procedure, cm^2	1.8 ± 0.2
Height, cm	167 ±5
Left ventricle size, mm	46 ± 0.2
Balloon size used, size mm, (n =47)	24, (45); 26(2)
Preprocedural mitral regurgitation (Gr 1), n	5
Preprocedural Pulmonary artery systolic pressure, mm Hg	84±10
Serum Creatinine, mg/dl	0.9±0.2
Atrial fibrillation, n	36
Periprocedural mortality, n	Nil

Table 2. Baseline characteristics of patients underwent patent ductus arteriosus closure.

Parameters	Values, n=12
Age, yrs.	17±7, median 19 (11, 43)
Sex, M/F	5/7
Diabetes, n	1
Hypertension, n	nil
Duration after coil or surgical closure, yrs.	10±3
Haemoglobin, gm/dl	11.1±0.7
Resting pulse rate, beats/min	74±5
Systolic blood pressure, mm Hg	126±8
Diastolic blood pressure, mm Hg	78±4

Table 3. Baseline characteristics of patients undergoing haemodialysis.

Parameters	Values, (n=17)
Age, yrs.	54±9
Sex, M/F	14/2
Diabetes, n	3
Hypertension, n	4
Left ventricular size, mm	47±2
LV posterior wall thickness, mm	10.6
LA size, mm	29±0.3
Duration of dialysis on the fistula, yrs.	4.5±2.1
Valvular heart diseases	Nil
Pulmonary artery systolic pressure, mm Hg	30±4
Systolic blood pressure, mm Hg	130±6
Diastolic blood pressure, mm Hg	84±10
Nifedipine, n	4
Prazosin, n	2
Haemoglobin, gm/dl	11±0.4

Figure legends

Figure 1: Shows the coronaries of a patient with rheumatic mitral stenosis (panels A, B, C and E) prior to balloon mitral valvuloplasty (panel D), magnification factor 17.

Figure 2: Angiogram in a patient with severe mitral stenosis prior to mitral valve replacement (magnification factor 17).

Figure 3: Shows the coronaries of a normal patient as control (panels A to C).

Figure 4: Shows LV angiogram in patients prior to undergoing Balloon mitral valvuloplasty (magnification factor 23).

Figure 5: Echocardiographic assessment of coronary arteries in short axis view. Upper panel shows pictures from patients with patent ductus arteriosus who underwent closure, and the lower panel shows pictures from patients on hemodialysis through peripheral arterio-venous (AV) fistula.

Figure 6. Echocardiography of a patient who underwent PDA closure in the past and the coronaries were dilated.

Figure 7. The echocardiographic pictures (short axis view) of some control patients and their coronaries.

Figure 8: The echocardiography in a patient with peripheral arteriovenous fistula on dialysis for chronic renal failure. The left ventricular dimensions are normal without hypertrophy and coronaries are dilated.

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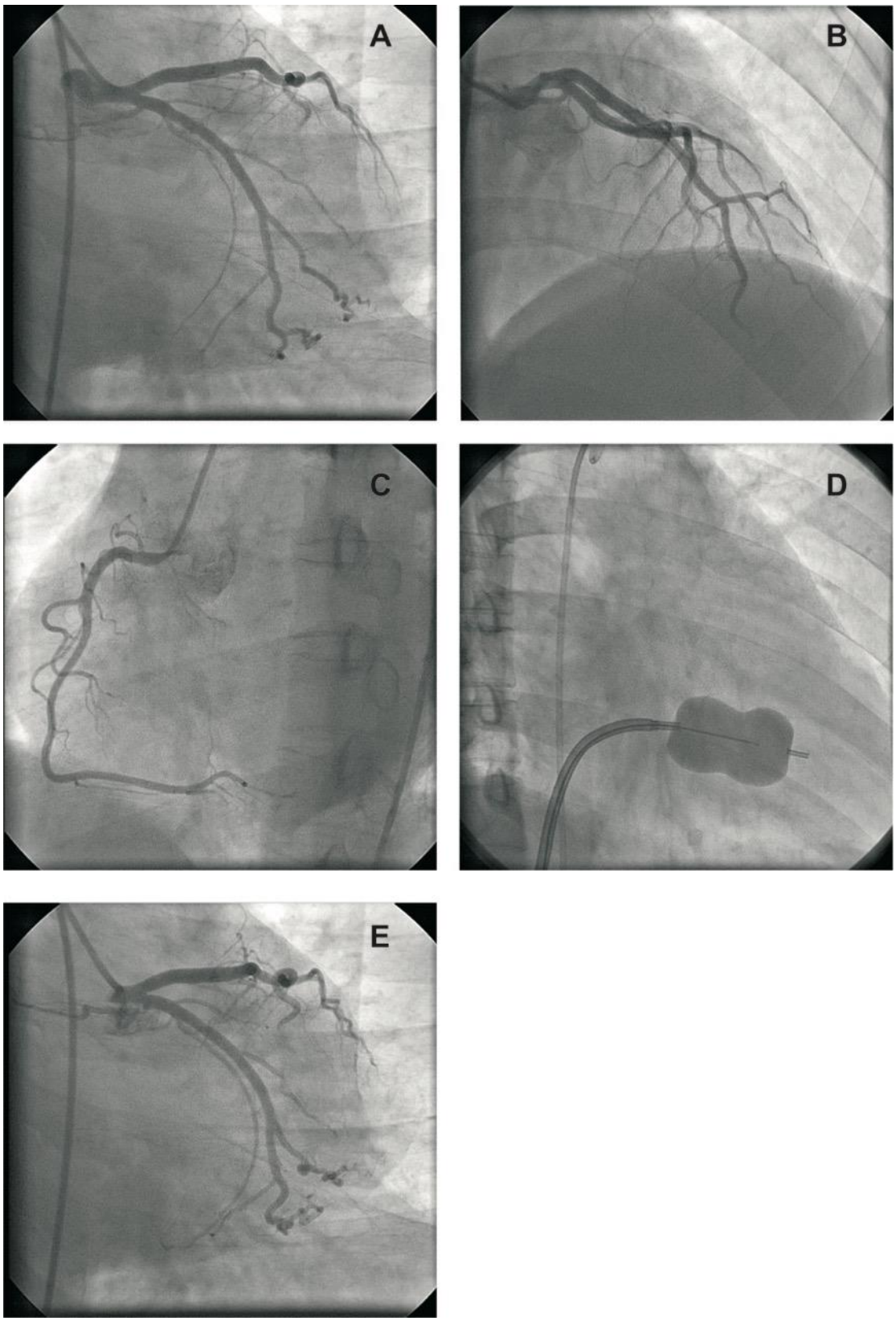


Figure 2. Angiogram in a patient with severe mitral stenosis prior to mitral valve replacement (magnification factor 17).

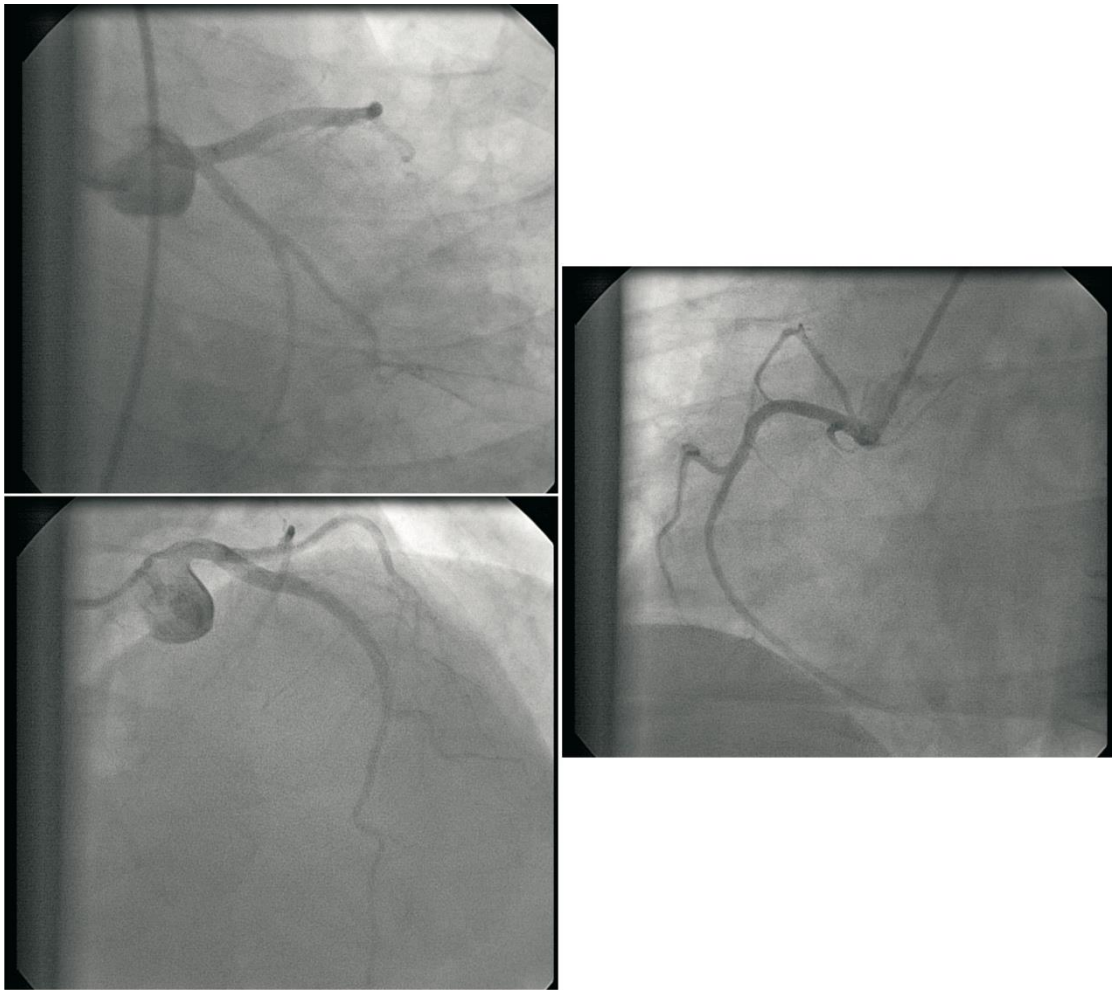
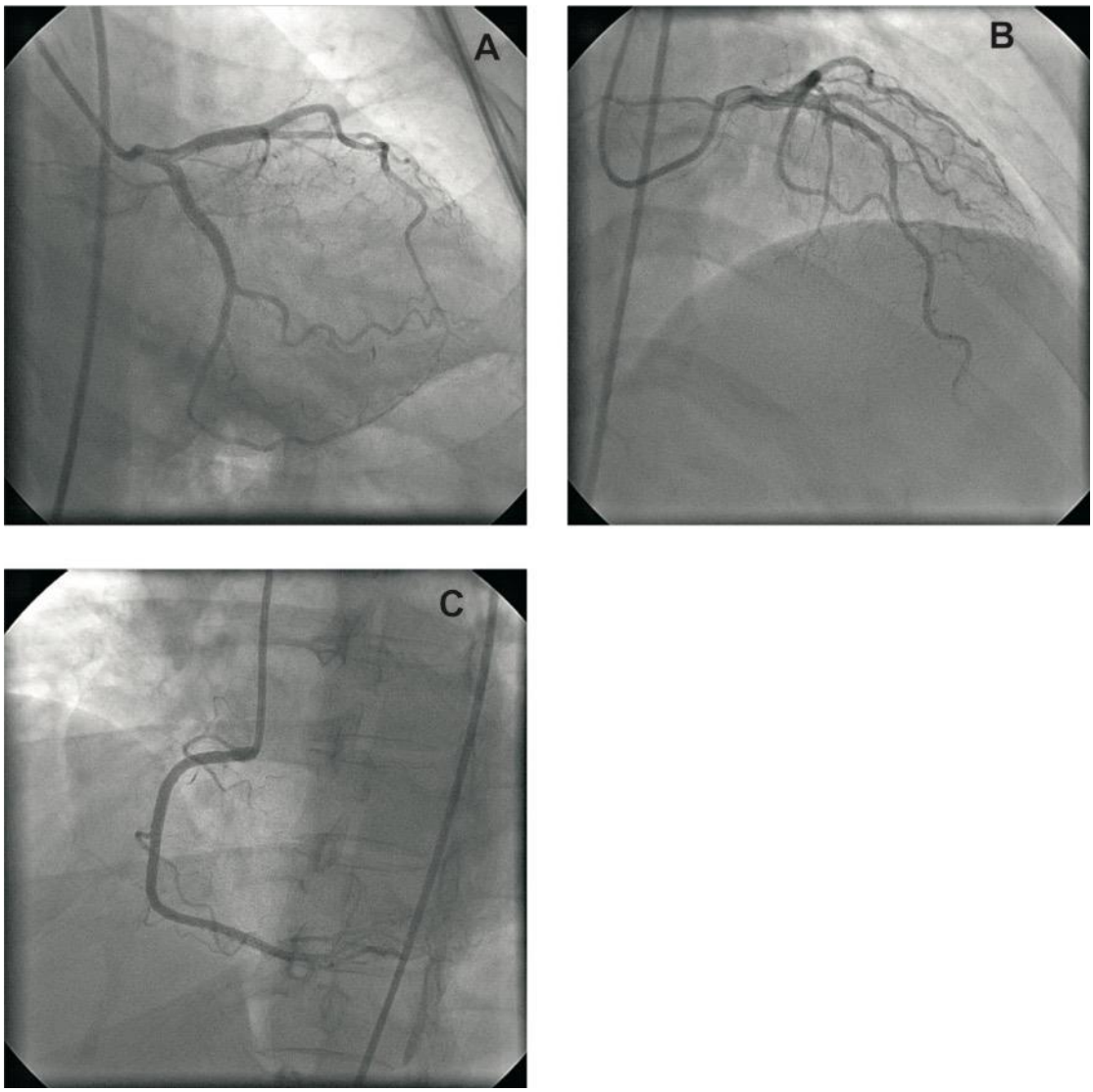


Figure 3 Shows the coronaries of a normal patient as control (panels A to C), magnification factor 17.



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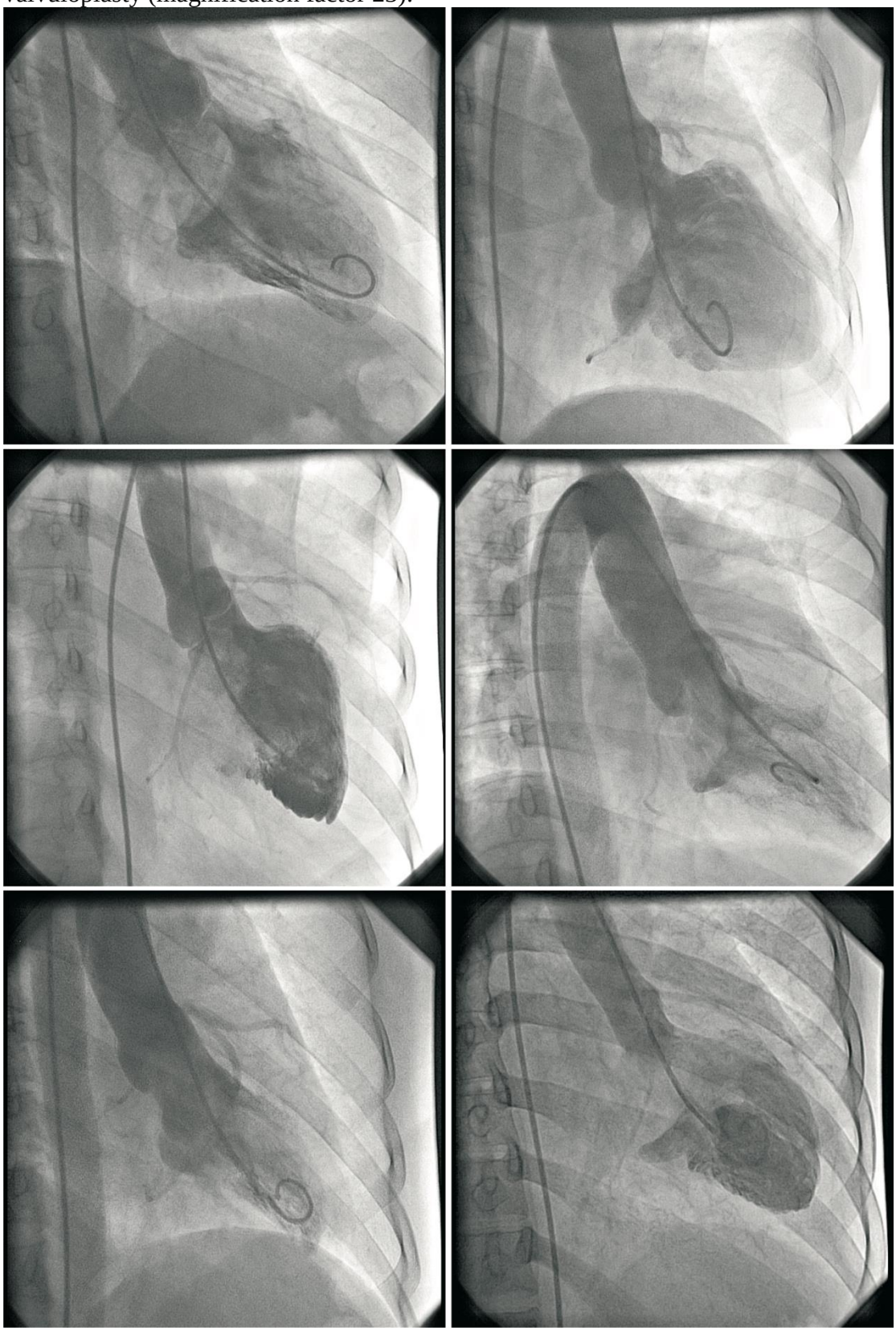

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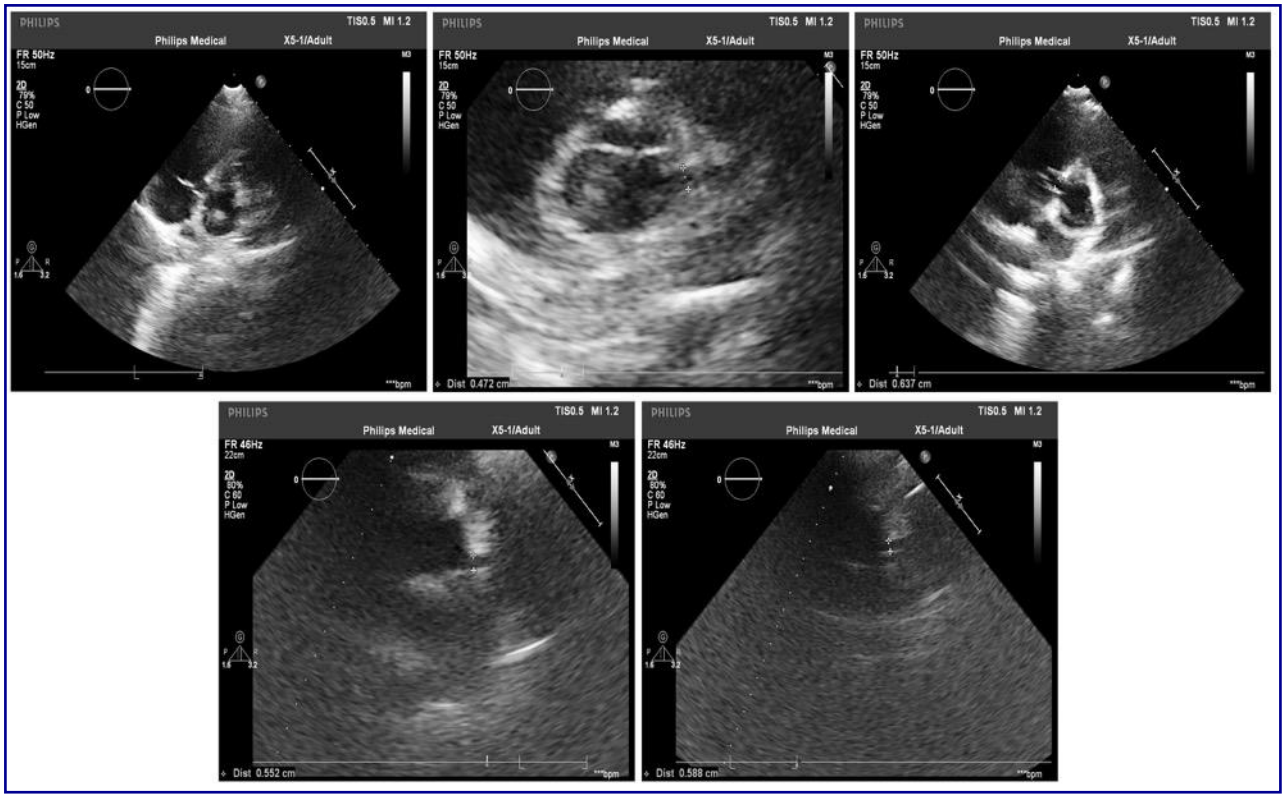

Figure 6. Echocardiography of a patient who underwent PDA closure in the past and the coronaries were dilated.

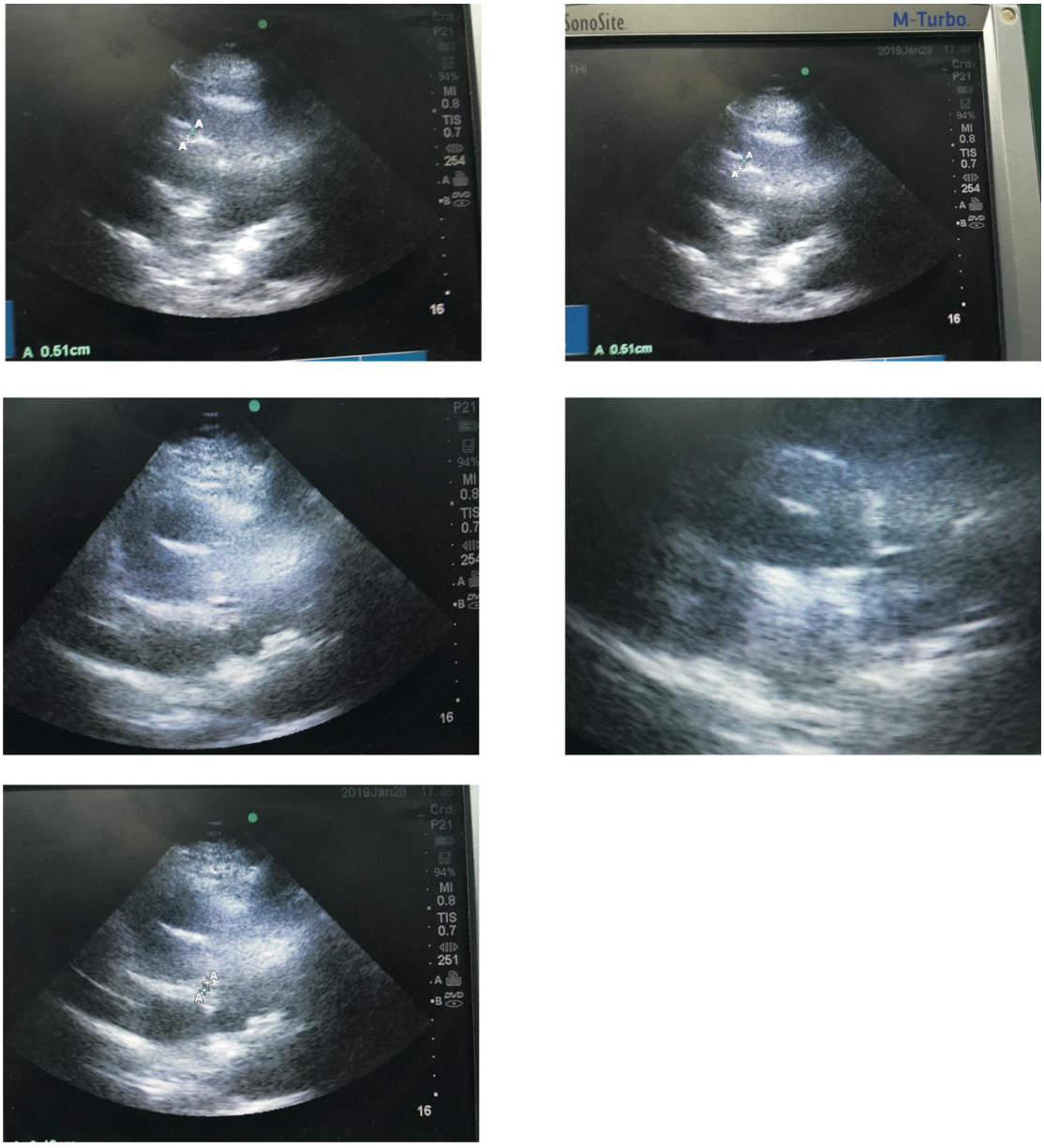

Figure 7: The echocardiographic pictures (short axis view) of some control patients and their coronaries.

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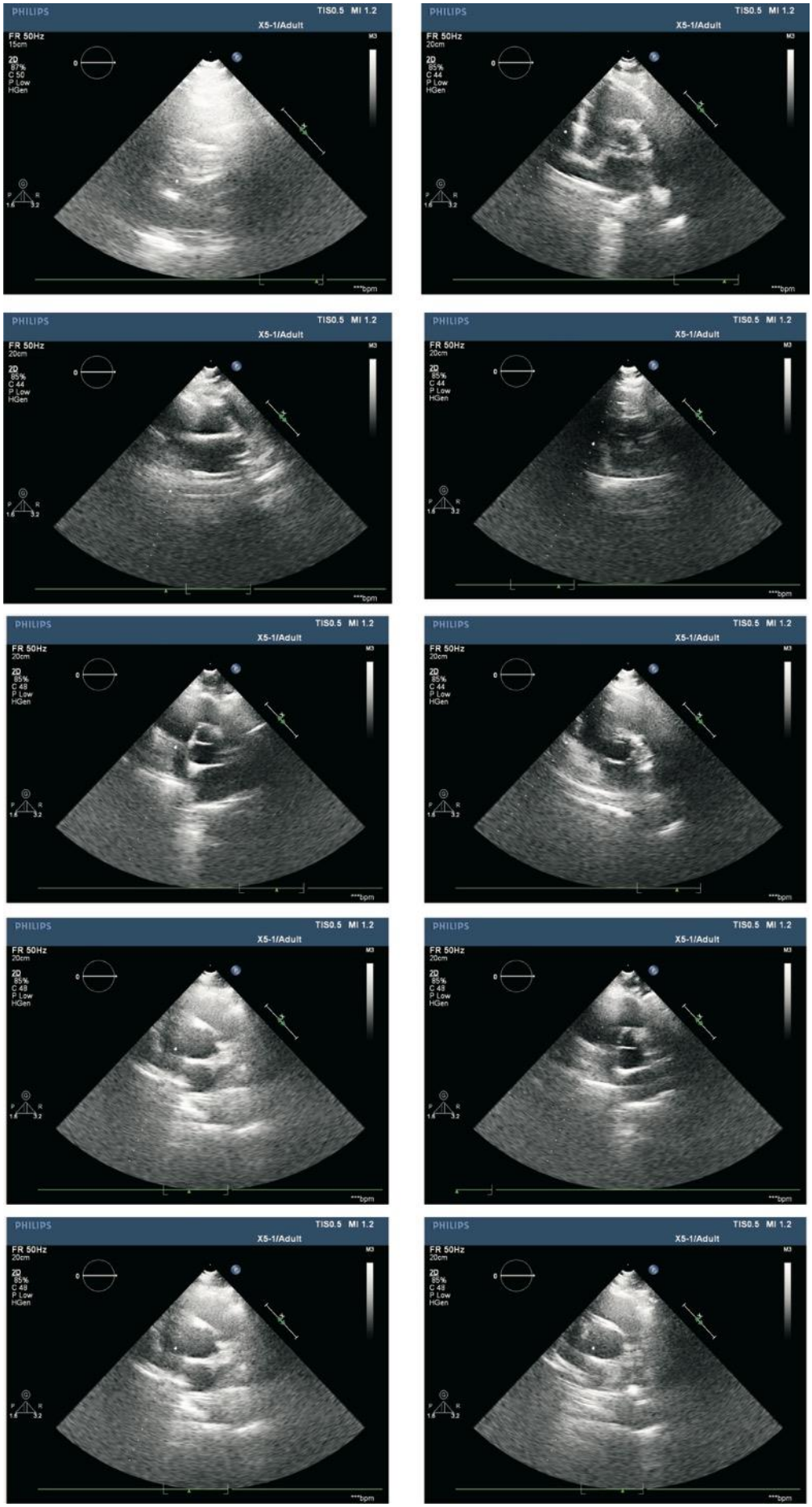
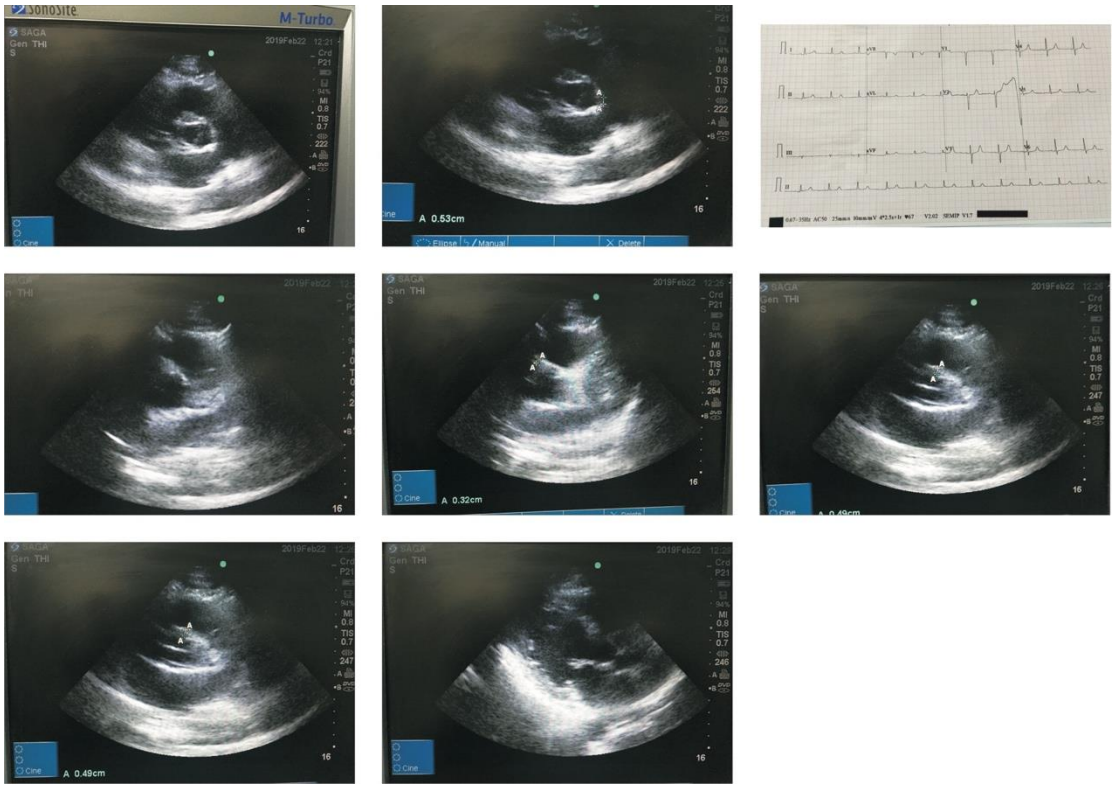


Figure 8: The echocardiography in a patient with peripheral arteriovenous fistula on dialysis for chronic renal failure. The left ventricular dimensions are normal without hypertrophy and coronaries are dilated.



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