

## Treadmill Testing- “Episodic Ischemia” in a Middle-Aged Woman Aged 46 years

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### 1. Abstract

The treadmill ECG stress test is commonly used as a screening test to identify myocardial ischaemia. During exercise, the physiological increase in heart rate is due to a decrease in vagal tone followed by an increase in sympathetic tone and the sufficient effort during treadmill ECG stress testing is defined as achieving 85% of the age-predicted maximal heart rate. The increase in sympathetic tone and vasodilation during exercise generally causes a rise in blood pressure. An exaggerated blood pressure response, defined as a peak systolic blood pressure of > 210 mmHg in men and > 190 mmHg in women was shown to predict the risk of hypertension in normotensive individuals, A drop in systolic blood pressure > 10 mmHg is an indication to terminate the treadmill ECG stress tests, as it could be due to myocardial ischaemia leading to left ventricular dysfunction. In addition to the evaluation of CAD, the treadmill ECG stress test is also often used to evaluate for chronotropic incompetency, in which the patient is unable to mount an adequate heart rate response to exercise, leading to symptoms such as effort-related dyspnoea and lethargy. The Bruce protocol is the most commonly used and it consists of a total of seven stages, with a gradual increment in the speed and gradient of the treadmill. Each stage lasts three minutes to allow the patient to acclimatise to the specific speed and gradient before advancing to the next stage. The MET value increases as the patient advances to higher stages of the Bruce protocol. Exercise intensity during the treadmill ECG stress test is calculated in METs, which reflect the amount of oxygen consumed per minute. 1 MET is equal to 3.5 mL/min/kg of oxygen used. Continuous ECG monitoring is carried out throughout the test and into the recovery period to assess for any changes in the ST segments due to limitation of coronary blood flow may lead to myocardial ischaemia, as well as for arrhythmia. The test is often stopped be-

fore completing Stage 7, when the patient achieves the target heart rate or is symptomatic, or when the test is positive. The duration of ST-segment depression is also important, as prolonged recovery after peak stress is consistent with a positive treadmill ECG stress test. Another finding that is highly indicative of significant CAD is the occurrence of ST-segment elevation > 1 mm (often suggesting transmural ischemia) and these patients are frequently referred urgently for coronary angiography.

A 46-year-old female developed anginal episodes during treadmill testing and further evaluation revealed a congenital coronary anomaly.

**2. Keywords:** Congenital coronary anomaly; Treadmill testing; Episodic ischemia; Angiographic imaging

### 3. Introduction

In normal condition, maintaining the normal coronary artery diameter is critical for myocardial perfusion and it changes continuously to maintain adequate oxygen delivery to the myocardial tissue. Coronary flow reserve defined as the ratio between blood flow at the maximum coronary vasodilation and is higher than 4 at normal condition. In patients with classic angina pectoris, diameter narrowing due to atherosclerosis results in significant reduction of coronary flow reserve. Thus, at resting status, sufficient myocardial perfusion may be possible; however, during exercise or emotional stress requiring adequate increase of cardiac output and myocardial oxygen demand, progressive coronary vasodilatation is limited due to fixed stenosis, resulting in development of myocardial ischemia or chest pain. Myocardial oxygen demand usually parallels with heart rate and the chest pain development due to classic angina pectoris usually aggregates in the daytime coinciding with the changes of the heart rate [1].

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Coronary artery vasospasm (CVS) is a transient and reversible vasoconstriction of the major epicardial coronary artery evoking myocardial ischemia and the development of chest pain, is not associated or parallel with increase of myocardial oxygen demand. Accordingly, variant angina is characterized by its circadian variation of development of chest pain or myocardial ischemia and there is no association with the heart rate. But the angina threshold in variant angina shows a typical diurnal variant with significantly lower level during nocturnal time or sleep when the heart rate usually shows lower level. Although resting chest pain is the usual clinical presentation of variant angina, in some cases, development of chest pain is associated with minimal effort such as walking in the morning; do not develop chest pain with more demanding exercise such as running in the daytime. This discrepancy between work loading and angina development represents typical diurnal or circadian variation of angina threshold in variant angina.

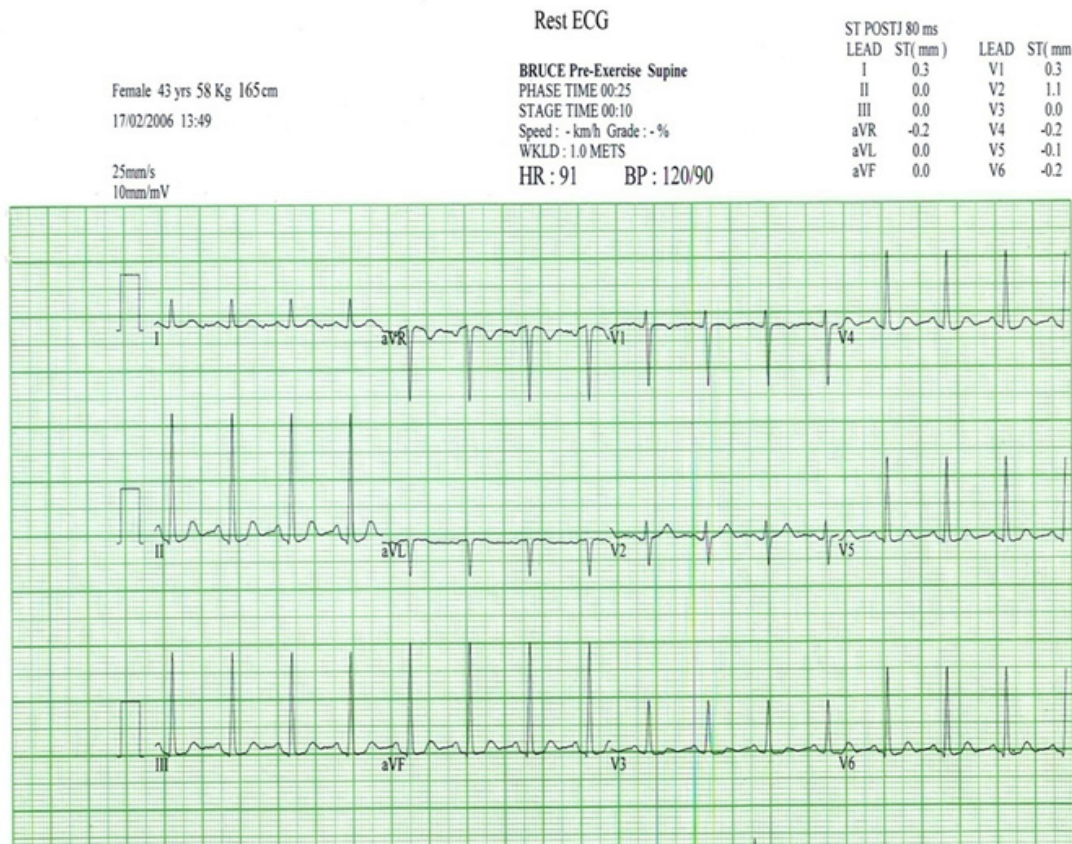
Episodes of myocardial ischemia during ambulatory activity in patients with stable coronary artery disease exhibits a marked circadian pattern, with the peak number of events occurring in the first few hours after awakening [2-4] and the majority of ischemic episodes are preceded by a heart rate increase [5]

Up to 20-30% of patients with angina-like chest pain have no flow-limiting epicardial coronary stenosis or spasm [6],[7], often defined as cardiac syndrome X [8] or microvascular angina [9], in

which coronary microvascular dysfunction occurs due to an inadequate coronary vasodilator capacity and/or enhanced coronary vasoconstrictor responses [10]. and can be detected by pacing-induced myocardial lactate production [11] or regional myocardial perfusion defects on single photon emission computed tomography or PET imaging [12],[13].The underlying mechanism of microvascular angina, suggests the involvement of blunted

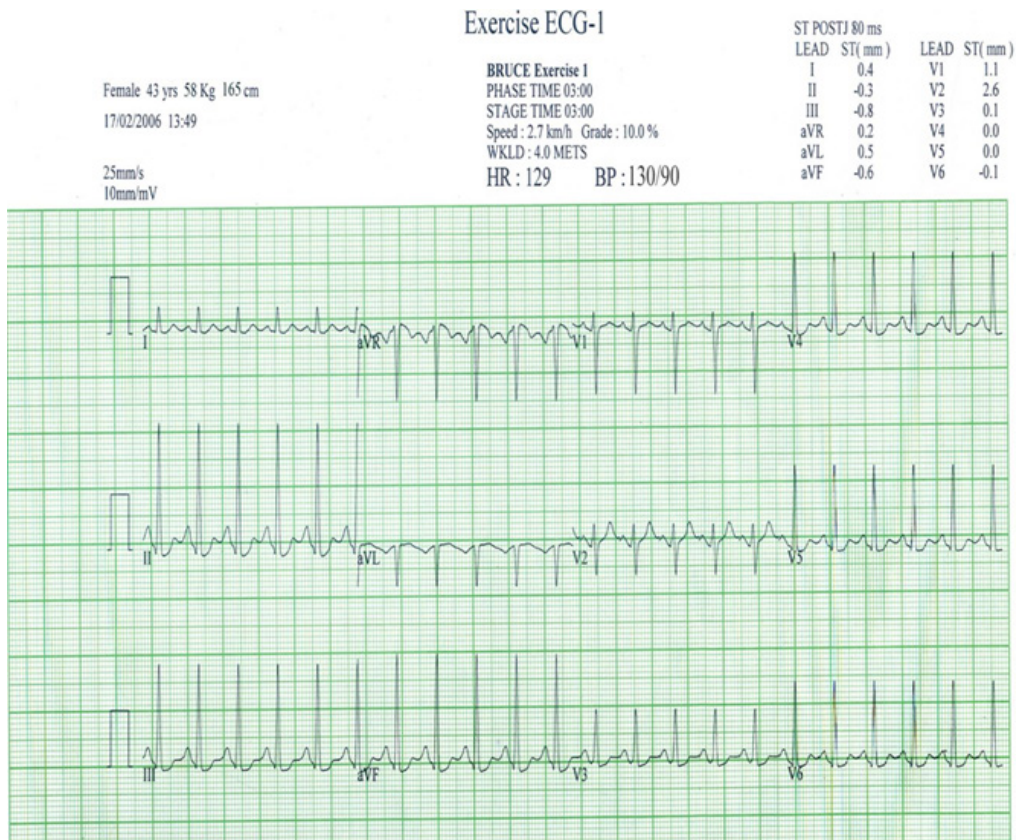
NO-dependent microvascular dilatation[14]. impaired EDHF(endothelium-derived hyperpolarizing factor) response, increased plasma levels of endothelin-1 (ET-1) and enhanced Rho-kinase activity as Rho-kinase has been identified as one of the effectors of the small GTP-binding protein Rho. Activated Rho-kinase down-regulates endothelial NO synthase, causing endothelial dysfunction [15]. and VSMC (vascular smooth muscle cells) hypercontractions.

Primary congenital coronary anomalies varies from 0.3% in necropsy series reported by Alexander and Griffith to 1.6% of patients undergoing cardiac catheterisation [16]. Clinical suspicion of coronary anomalies remains an important challenge and often discovered as an incidental finding during cardiac assessment and their clinical significance varies greatly across different variants [17]. Most of these anomalies are of little clinical significance during childhood and may become important in adolescence and young adult life when extremes of physical exertion may cause significant intolerance of the previously well tolerated malfunction [18] and so this case has been reported (Graph 1-8).

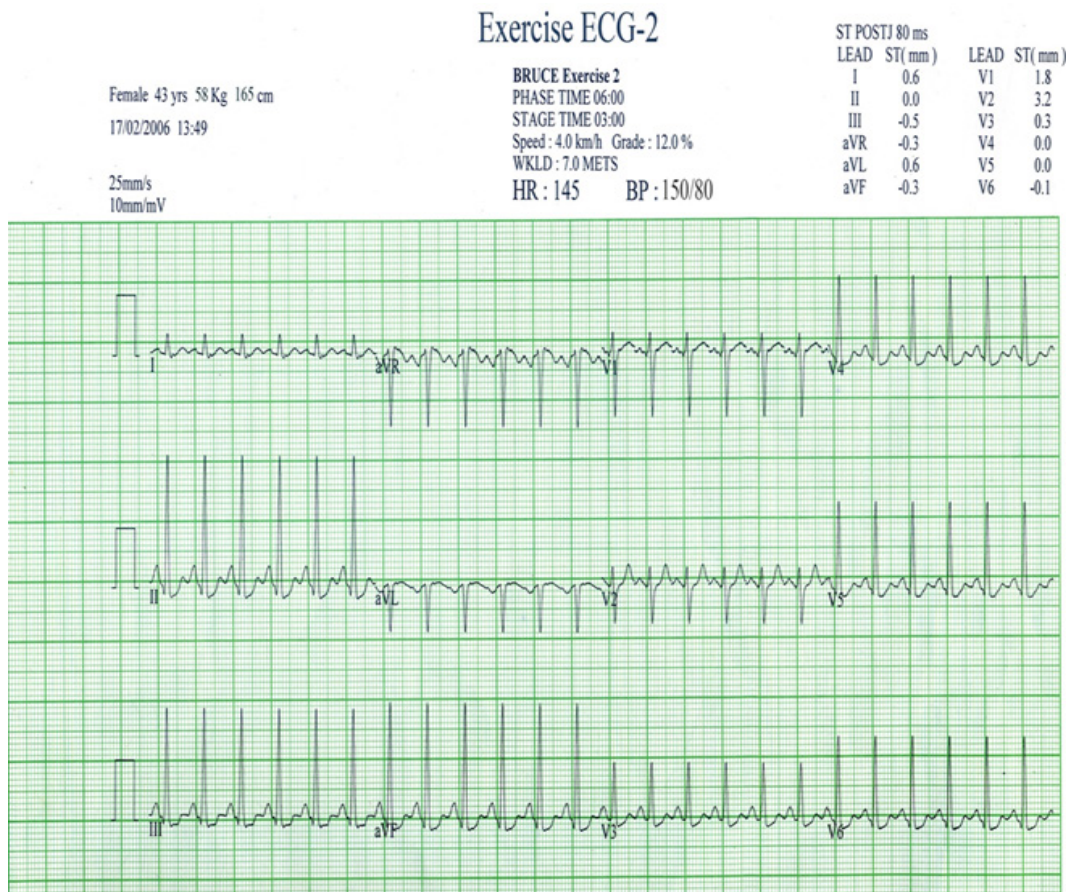


Graph 1: (Rest ECG showing no ST-T changes)



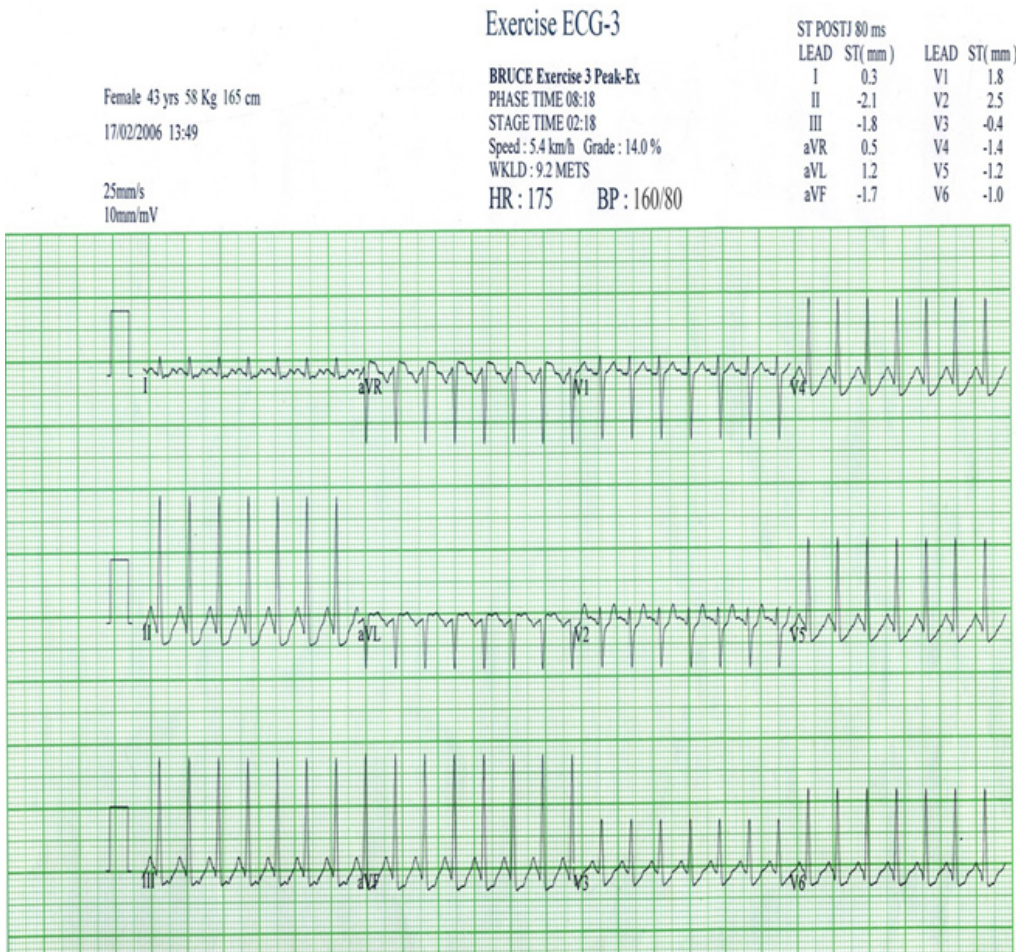


**Graph 2:** (Exercise ECG- Stage 1 showing 1 mm junctional ST depression in inferior leads (L II, III, aVF) and precordial leads - V<sub>4</sub> to V<sub>6</sub> according to increase in heart rate)

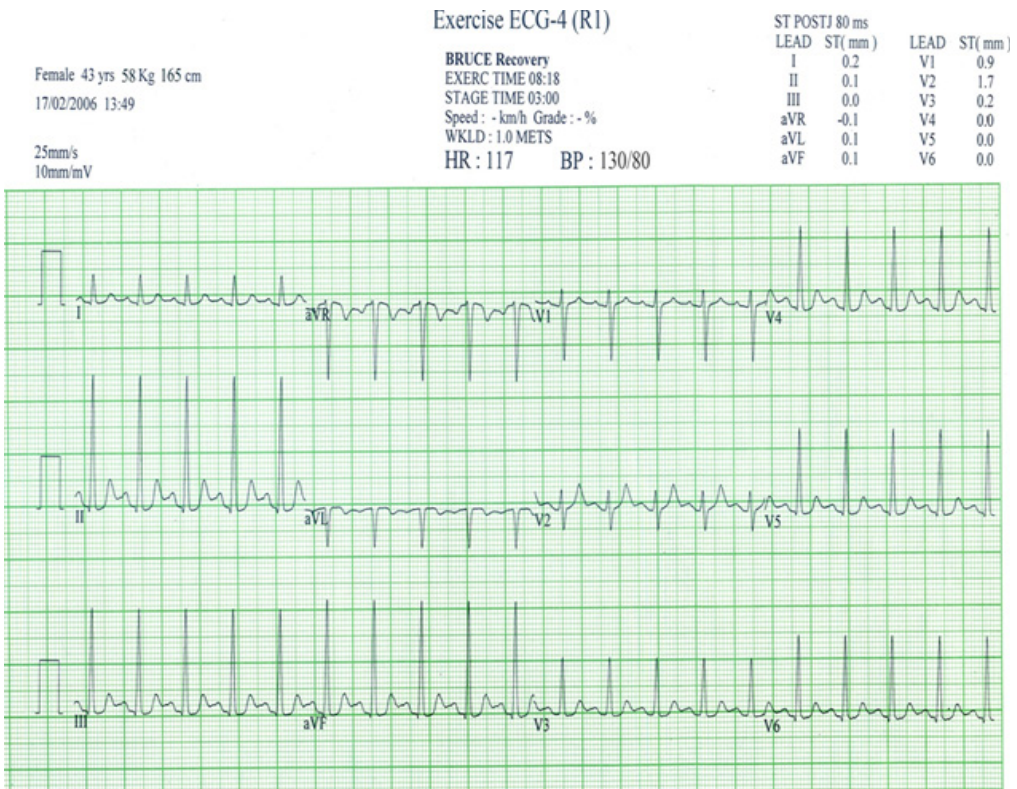


**Graph 3:** (Exercise ECG stage 2 showing the junctional ST depression becoming “upsloping” in inferior and precordial leads according to progressive increase in heart rate)



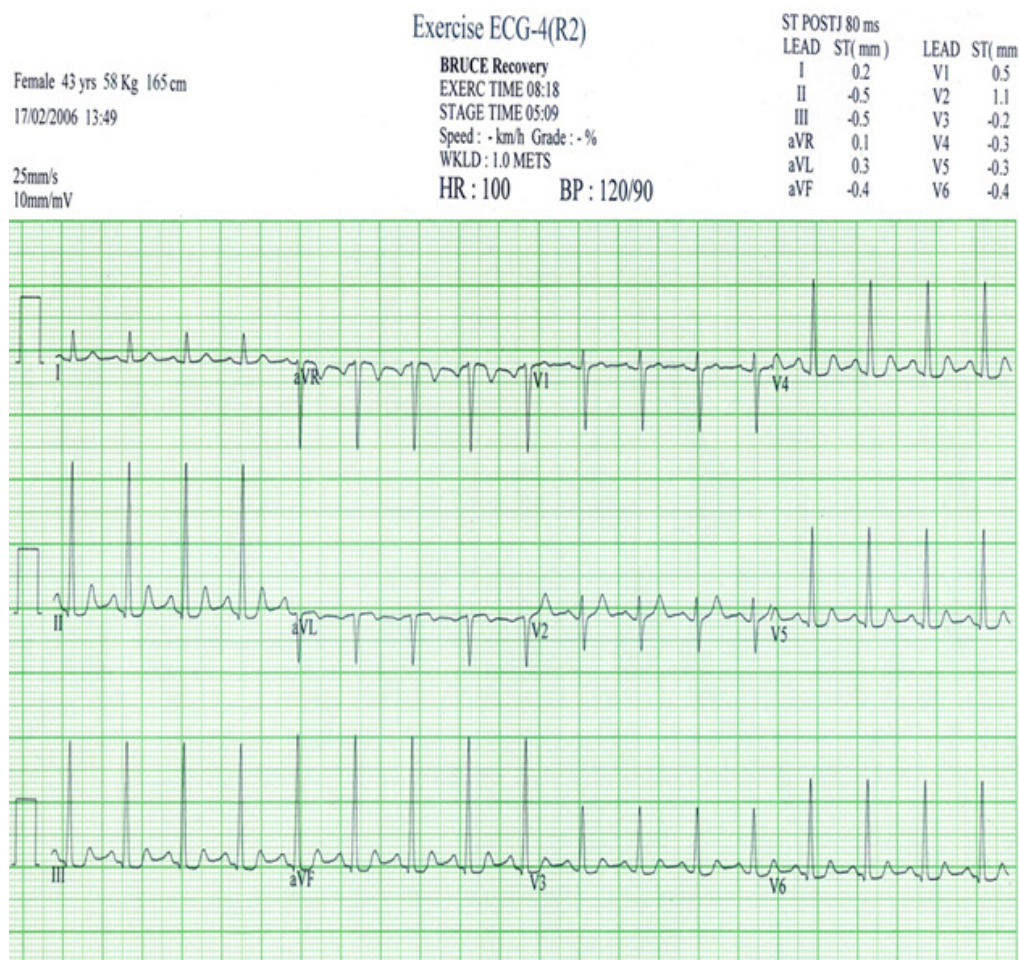


**Graph 4:** (Exercise ECG- Stage 3 at peak exercise showing the junctional (J point) ST depression becoming “rapid upsloping” in inferior and precordial leads)[19] suggesting “episodic ischemia” due to increase in heart rate.)



**Graph 5:** (Exercise ECG in Recovery stage 1 showing the rapid normalisation of ST segment in inferior and precordial leads)





**Graph 6:** (Exercise ECG in Recovery stage 2 is becoming similar to Rest ECG)

#### 4. Case Report

A 46 years old female medical practitioner was rushed to the emergency department with sudden onset of chest discomfort while she was climbing the staircases in a shopping complex. She is diabetic (sugar status under control), not hypertensive and previously asymptomatic. Clinically, she is anxious and her heart rate is initially 110 bpm and later became normal. Blood pressure was in the normal range and ECG, X-Ray chest were normal. Echocardiography revealed no associated cardiac defects. She was symptom free shortly without any medications. She was admitted in the intensive care unit for observation and thereafter no further episodes of chest discomfort. Holter monitoring was normal. Blood chemistry including Thyroid function tests revealed no abnormalities. After 48 hrs observation, she was subjected to Treadmill exercise test which is as follows

She has achieved 9.2 METS in Bruce protocol stage 3 at peak exercise and developed chest discomfort with sweating and the test was stopped. The ECG in stage 3 at peak exercise revealed junctional ST depression with rapid up sloping of ST segment which immediately

returns to normal as shown in ECG 4 R1, R2 in the recovery period suggesting the exercise induced “episodic ischemia”.

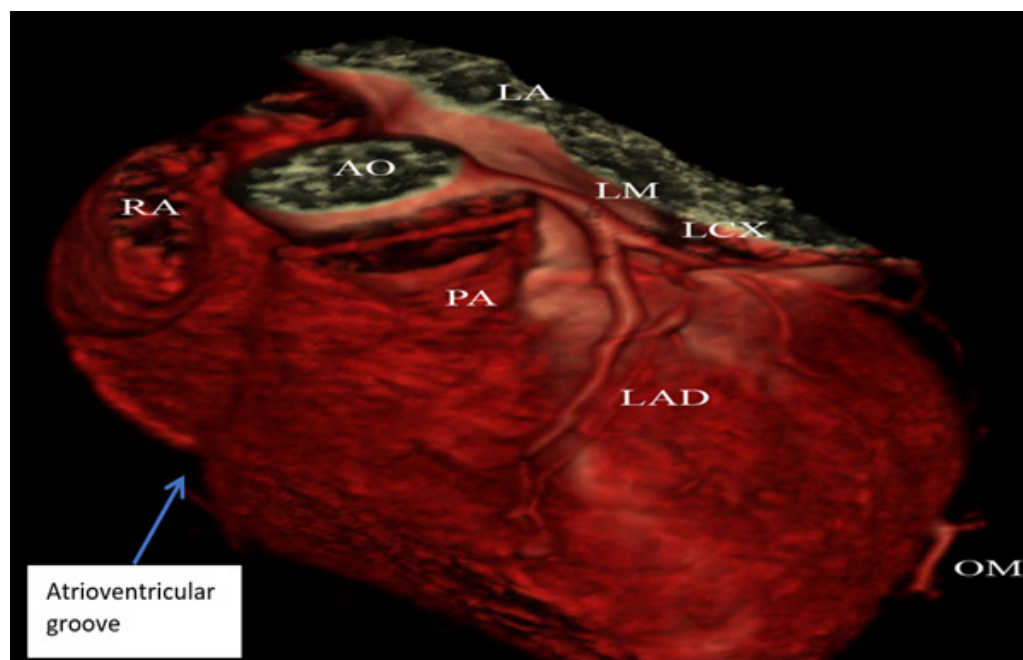
she was advised cardiac CT angiography as a screening test which is shown in Figure 1.

The CT images, Figure 1 shows “Right coronary artery is not visualized in the Right AV groove” and no anomalous vessel is passing either anterior to the pulmonary artery or in between pulmonary artery and aorta.

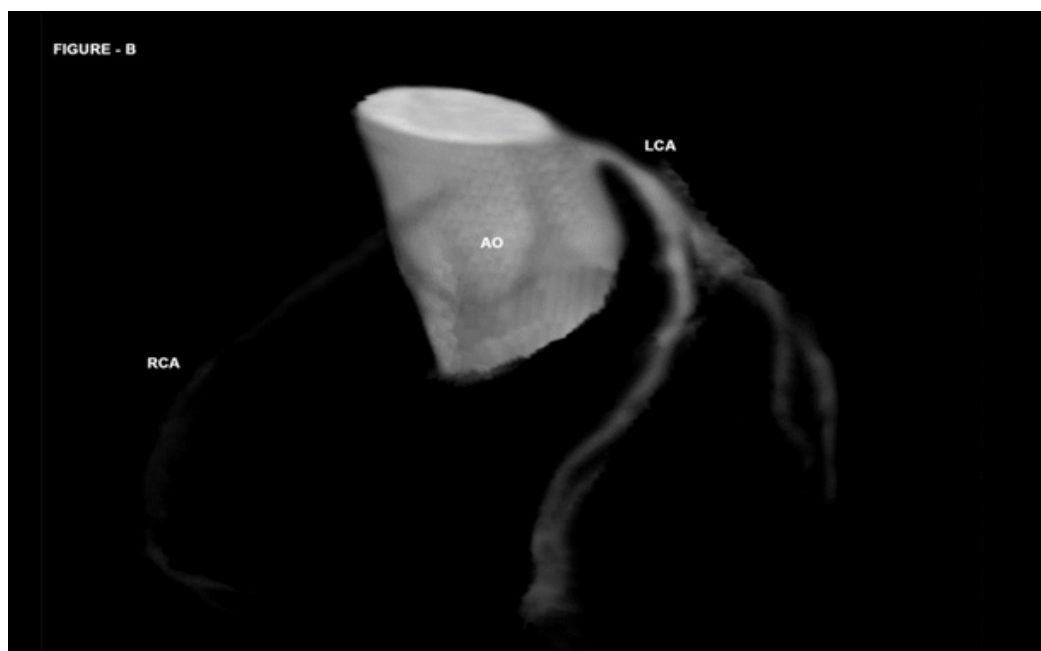
Cardiac MR angiography which is shown in Figure 2 revealed non visualization of the clear cut origin of Right coronary artery from the aortic root and trifurcation of left coronary artery (Figure 3).

Then, she was advised to invasive coronary angiography as shown in Figures 4 to 8.

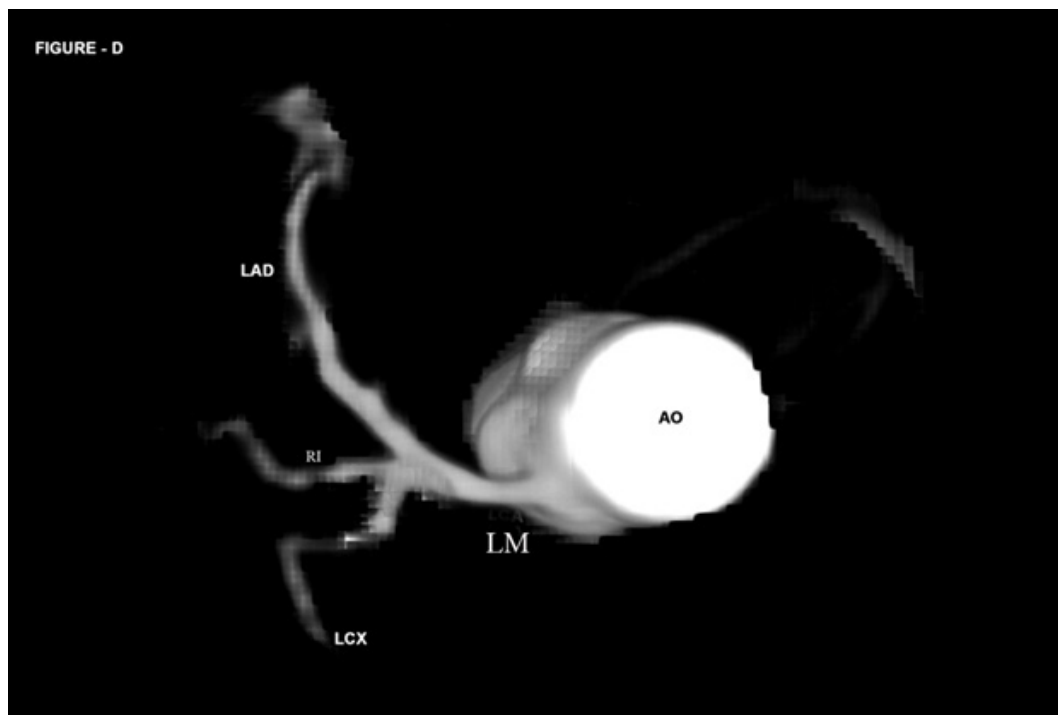
The Figures 4 to 8 revealed “Left circumflex coronary artery is continuing to form the Right coronary artery”, a rarest coronary anomaly [20], [21]. The Runs of the coronary angiogram revealed retrograde filling of Right coronary artery as a continuous flow from Left circumflex and there is a delayed filling in the proximal portion of the Right coronary artery.



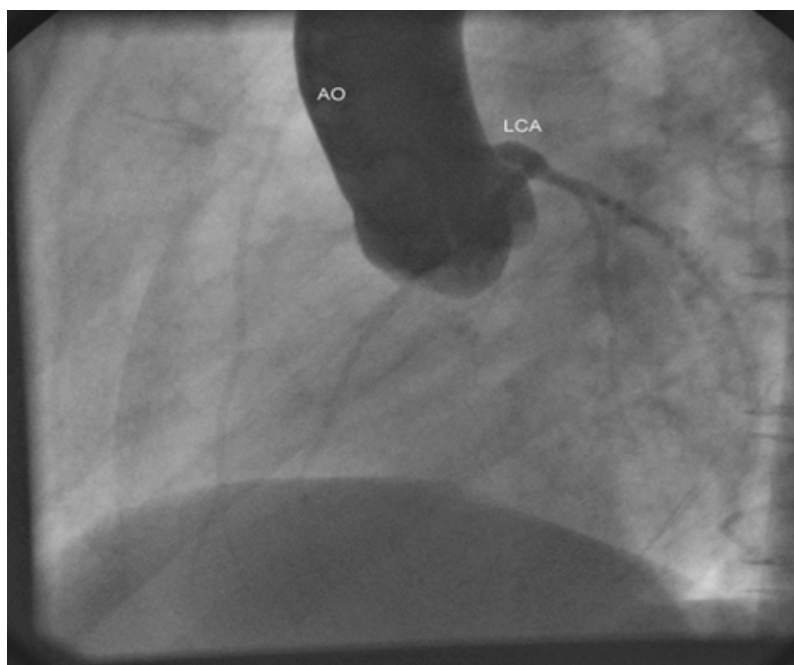
**Figure 1:** showing no anomalous vessel between aorta and pulmonary artery. Blue arrow shows no vessel in the right atrioventricular groove



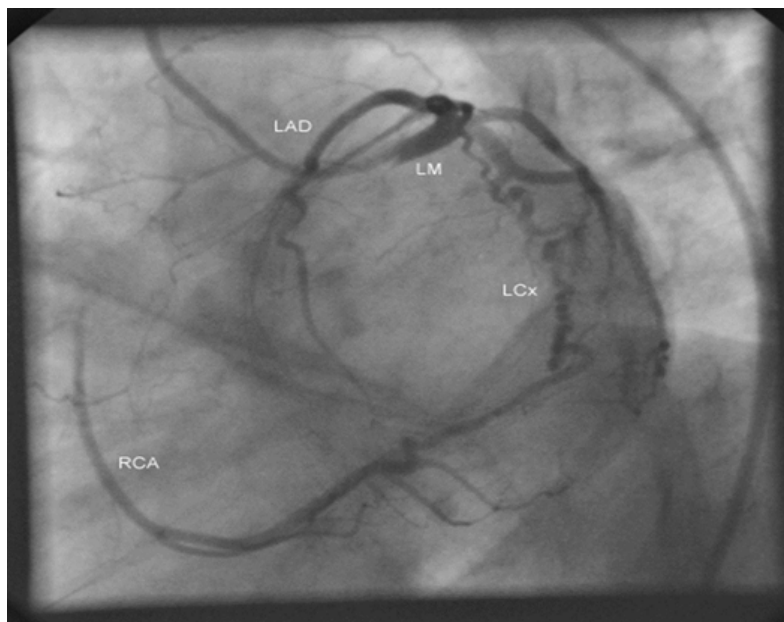
**Figure 2:** shows the impression of Right coronary artery with no clear cut lumen and origin from the aortic root



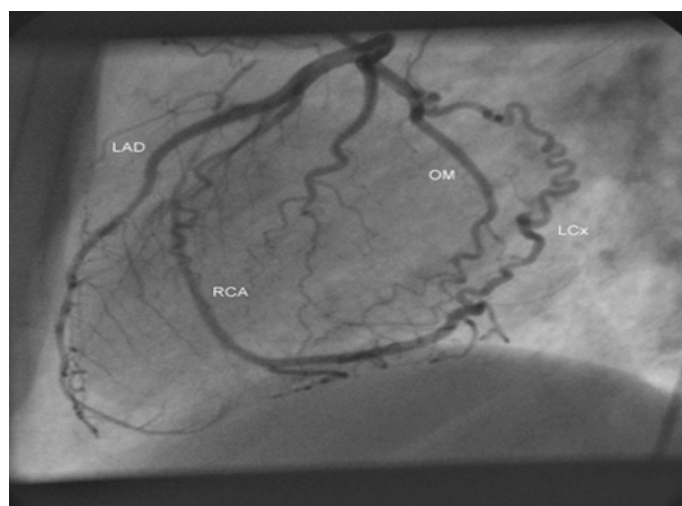
**Figure 3:** shows the Left main trifurcates into LAD (left anterior descending artery), RI (ramus intermedius) and LCX (left circumflex coronary artery)



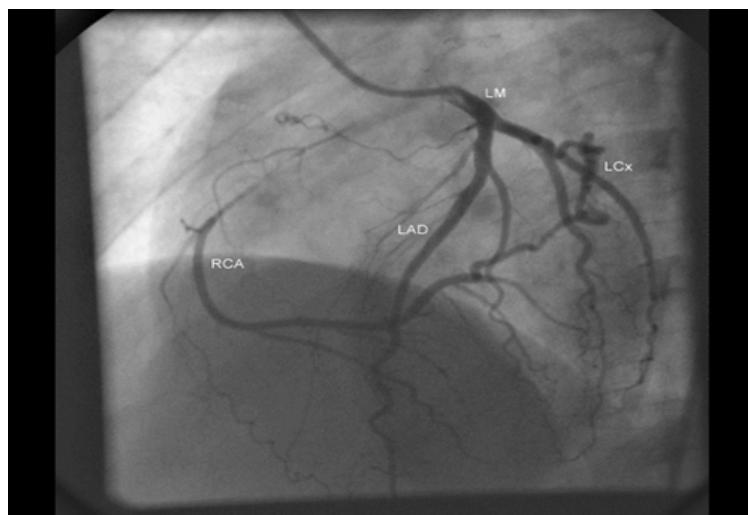
**Figure 4:** shows aortic root angiogram which revealed non visualization of the origin of Right coronary artery from the aortic root.in LAO cranial view.



**Figure 5:** shows LCx (left circumflex coronary artery) is continuing to form the Right coronary artery (RCA) in “spider view” (LAO caudal).



**Figure 6:** showing the Type III LAD (left anterior descending artery wraps around the cardiac apex into the posterior interventricular groove and LCx (left circumflex coronary artery (tortuous vessel) is continuing to form the RCA (right coronary artery). Red arrow shows the “Proximal RCA” in left lateral view.



**Figure 7:** shows the LCx (left circumflex coronary artery is continuing as Right coronary artery) in LAO cranial view.





Figure 8: showing the tortuous left circumflex coronary artery (LCx) in RAO caudal view

5. Discussion

5.1. Review of literature

Angelini et al. described a wide range of anatomical variants [22, 23] and the first classification of CAAs (coronary artery anomalies) is\ was proposed by Ogden in 1969 as three categories: as minor , major and secondary anomalies [24]. According to Angelini, the following characteristics are considered as normal [25-28] as shown in Table 1. In 2000, Dodge-Khatami et al. introduced a new system of nomenclature used to record anomalous aortic origin of a coronary artery

in order to develop guidelines for its treatment and monitoring [29]. In 2003, a new classification emerged, proposed by Rigatelli et al., groups into seven categories [30] as shown in Table 2. In 1962, an anomalous left coronary artery originating from right coronary sinus was described in a healthy boy found dead after a cross-country race. Later, in 1974, Cheitlin et al. demonstrated that several autopsied patients with anomalous origin of coronary arteries from the opposite sinus had experienced sudden death [31]. Brothers et al. presented the first case series of families with an interarterial course in the pediatric population [32]

Table 1: Normal anatomical variants of coronaries

S.No.	Normal variants
1	two to four ostia, in the right and left coronary sinuses
2	proximal orientation of 45° to 90° from the aortic wall
3	a common trunk, located on the left, giving rise to the left anterior descending artery and circumflex artery
4	a middle subepicardial segment, with branches appropriate for the dependent myocardium
5	termination of the entire system in a capillary network

Table 2: Rigatelli classification of anomalous coronaries

S,No	Categories
1	Hypoplasia / atresia
2	a single coronary artery (hyperdominance)
3	fistula
4	originating from other arteries
5	originating from the wrong coronary sinus
6	splitting (separate origins from the left anterior descending artery and circumflex artery)
7	tunneling

## 5.2. Etiopathogenesis

During fetal development, vascular sinusoids develop within the embryonic myocardium and when it becomes more compact, the sinusoids disappear and a network of veins, arteries and capillaries develops. These vessels connect with other mediastinal vessels at approximately 32 days of gestation. The primitive coronary vessels appear around the seventh week of gestation, after the formation of the aorta from the division of truncus arteriosus. As the coronary artery network develops, endothelial buds appear at the base of the truncus arteriosus and later join with the coronary artery network, which develops from the sinusoids and establishing the definitive coronary artery circulation [33, 34].

Embryologically, the subepicardial vessels derive from extracardiac epicardial cells, which form a plexus like vasculature, invading the myocardium and growing towards the aortic root to the facing aortic sinuses. At the time of spongy myocardium, intramural blood supply directly from the ventricular cavities through the intertrabecular spaces lined by the endocardium, whereas later, at the time of myocardial compaction, vascularization originates from the subepicardial network. The connection of the subepicardial plexus with the aorta occurs with prongs of the peritruncal ring which penetrate the facing aortic sinuses and the septation of truncus arteriosus is not responsible for the final position of the coronary orifices. "Peritruncal ring" is a subepicardial network of cells ("bioepicardial organ") surrounds the orifices of the great arteries and eventually connects with the facing aortic sinuses.

In "outgrowth hypothesis", the development of sprouts or buds from the aortic wall of facing sinuses, capturing the peritruncal ring of coronary subepicardial arterial vasculature [35, 36]. The "ingrowth hypothesis" is supported by the observation that the prongs of the peritruncal ring penetrate the aortic wall and make contact with the endothelial lining of the aorta [37, 38]. Recent investigations confirmed that the proximal coronary arteries do not grow from the aorta and they grow into the aorta from the peritruncal ring of the subepicardial vascular plexus [39]. Formation of the left coronary artery precedes the right coronary artery and different from the tunica media of the ascending aorta as the tunica media of the coronary arteries does not derive from the neural crest.

Cellular cross talks and signaling pathways such as notch and hippo signals, transcription factors, angiogenic molecules, and apoptosis take place [40-44] and VEGF plays a crucial role in the development of coronary ostia and main stem formation [45]. Absence of VEGF was shown to inhibit ostia formation. Epicardial inhibition, reducing apoptotic remodeling at the ventricular-arterial junction, alters vascular connection with the aorta and may produce coronary artery anomalies observed in humans [46]

## 5.3. Molecular hypothesis

Analysis of signalling molecules and transcription factors pivotal to CA (coronary artery) embryogenesis have been recently proposed. Wt1 (Wilms tumour suppressor gene)-dependent disruption

of retinoic acid synthesis in the epicardium directly or indirectly down-regulates the expression of Pdgf receptors  $\alpha, \beta$  in EPDCs (epicardial-derived cells) [47], interfering with coronary smooth muscle progenitor cell differentiation. The Notch/Delta cell-to-cell signalling pathway promote arterial endothelium during coronary blood vessel development [48], [49]. Down-regulation of the nuclear transcription factor Coup-tf II (COUP transcription factor 2), a Notch repressor [50] and up-regulation of Ephrinb2 expression in CA progenitor cells also correlate with CA endothelial specification. Myocardium-secreted Fgfs and Vegf participate in the regulation of coronary endothelial cell and vascular assembly [51] and Vegf (Vascular endothelial growth factor) has been reported to be dependent on myocardial Fgf (fibroblast growth factor) -induced Hedgehog activity [52]. Coronary morphogenesis is linked to the growth and compaction of the ventricular walls since hypoxic gradients in the ventricular walls activate myocardial Vegf and promote endocardial sprouting in CA development [53]. Cell membrane-bound Ephrins [54] and Semaphorins [55] provide attractive cues to the developing coronary endothelium, thus patterning its growth over the myocardium.

The aortic root is important in defining the connections of the LCA and RCA stems to the proper coronary Valsalva sinuses of the aorta. Interestingly, the CXCL12/CXCR4 signalling axis has been recently implicated in proximal CA connection with the aortic endothelium [56]. Developmentally, the 'proximal' aorta and the 'distal' cardiac chamber coronary vascular plexus are two distinct elements and any genetic factor preventing the correct assembly of these two elements is likely to result in CA anomalous connection. The specific location of the aortic root in the cardiac base, ultimately determines the path followed by coronary stems with respect to the aortic and pulmonary roots, the proximity of the coronary sinuses to the anterior interventricular and atrioventricular grooves probably contributing to the specific location of the two main coronary stems [57]. The formation of the main CA tracts correlates with the areas where the epicardium and associated subepicardial matrix first form [58] which is consistent with the subepicardial association of cardiac fat and CAs (coronary anomalies), that partially, originate from the embryonic epicardium [59].

## 5.4. Episodic myocardial ischemia

Intramural course of the coronary arteries [60], [61] is considered a variant of normal when covered by a myocardial bridge. and may be the cause of myocardial ischemia if completely surrounded by a sleeve of the myocardium with disarray and an intramyocardial course at least 2.5 cm long and 0.5 cm deep has been documented [62]. In young people, under 35 years of age, the major objective is sudden death and in those over 35 years of age is myocardial ischemia. Exercise-induced ischaemia has been attributed to tachycardia (episodic) due to increase in myocardial oxygen requirement and a reduction in the diastolic coronary flow [63] and the mechanisms that produce ischemia in CAAs are shown in Table 3.



Table 3: Mechanisms that produce ischemia in CAAs

1	Angulation of the anomalous artery	In contrast to a normal coronary artery, which is perpendicular to the aorta at its origin, the anomalous coronary artery may bend over itself to reach. Because of this, the ostium of the anomalous coronary artery would be smaller, with valve-like ridges, as compared to the normal circular ostium, and could become compressed in the case of a marked expansion of the aorta, such as that observed during strenuous exercise [64]
2	Initial course of the CAA.	(a) interarterial, between the aorta and pulmonary artery, the increase in the pressure in the 2 vessels, occurring during exertion, would produce a compression of the anomalous coronary artery [65].  (b) intramural, the obstruction may be enhanced since the coronary artery can become deformed within the aortic wall during periods of hypertension [66]
3	Spasm in the anomalous coronary artery	as a result of endothelial damage produced by the anomalous pathway [67]
4	Intussusception	the proximal portion of the CAA in the aortic wall [68].

5.5. Microvascular Angina

The endothelial monolayer can administer the exchange of fluids and metabolites and, furthermore, can manage vascular hemostasis. In case of a raised myocardial metabolic request, the coronary microvasculature modulates the peripheral vascular resistance and administrates the blood flow distribution that can reach a fivefold increase in healthy subjects.

The coronary microcirculation is an adaptive system that regulates myocardial perfusion [69], the epicardial coronaries (diameter > 400 μm) act as transport vessels, and the pre-arterioles and arterioles mainly determine the resistance. The autoregulation of this resistance makes it possible to maintain a constant blood flow over a wide range of coronary perfusion pressures, delivering oxygen and nutrients to the tissues and removing waste products. Several mechanisms play a role in this autoregulation, namely: myogenic regulation by the vascular smooth muscle cells, metabolic control by metabolites from adjacent myocardial cells, endothelial function responsive to changes in vascular wall tension, autonomic innervation, and circulating hormones including endothelium dependent relaxation factors such as nitric oxide (NO) and prostaglandins [70] and vasoconstrictor agents such as histamine, norepinephrine, and serotonin [71].

Coronary vascular dysfunction can be caused by functional (endothelial & non-endothelial) [72] and structural abnormalities. Endothelial function can be evaluated by the response of the coronary arteries to acetylcholine. If coronary vasodilation occurs after administration of acetylcholine, reflects a well-functioning endothelium and if vasoconstriction occurs, it indicates endothelial dysfunction, which is often found in the early phase of atherosclerosis [73]. Non-endothelial mediated functional abnormalities are related to decreased diastolic time, increased intramyocardial and intracavitary pressures, and/or tissue edema. Structural abnormalities include microvascular remodeling in arterioles (intimal thickening, smooth muscle cell proliferation and perivascular fibrosis) and decreased capillary density resulting in increased microvascu-

lar resistance, seen in left ventricular hypertrophy, calcium surplus and amyloidosis. The non-endothelial mediated functional and/or structural abnormalities of the coronary microcirculation can be assessed by CFR and microvascular resistance measurements.

Camici and Crea defined CMD (coronary microvascular dysfunction) as four types [74, 75] as shown in Table 4.

The two primary NPs (Natriuretic peptides) are the atrial natriuretic peptide (ANP), released when atrial wall stretching occurs, and the brain natriuretic peptide (BNP), secreted by ventricular myocytes in case of volume overload. Furthermore, the N-terminal prohormone of BNP (NT-proBNP) has an established role and clinical use as a biomarker. Both NPs control fluid homeostasis, natriuresis and express dose-dependent vasoactive effects. ANP is essential for endothelial homeostasis through autocrine and paracrine secretion. Patients presenting both CMD and left ventricle (LV) diastolic dysfunction showed increased levels of plasma NT-proBNP compared to healthy subjects. The association of low CFR and high Tn (Troponin) levels was related to an increased incidence of major adverse cardiovascular events (MACEs)

Microvascular angina (MVA) due to CMD is difficult to distinguish from classic angina due to obstructive CAD because both are often exercise-related. MVA is more likely if the angina continues after exercise cessation, starts after exercise and/or has limited response to nitroglycerin administration and more often triggered by palpitations or mental stress [76]. The intensity of symptoms can vary over time and can be so severe that patients are limited in daily life activities. Angina at rest often occur in addition to exercise-related complaints [77] due to a vasospastic component of coronary vascular dysfunction [78]. Pure vasospastic (Prinzmetal) angina usually occurs at rest, mainly at night and/or early morning, however, exercise-related symptoms can also be due to vasospasm[79, 80].

The gold standard to diagnose coronary vascular dysfunction is an invasive coronary vasomotor test that can comprehensively test all 4 endotypes of coronary vascular function: epicardial and microvascular coronary vasospasms, vasodilatory capacity and microvas-

cular resistance. Coronary vascular dysfunction (Coronary Vasomotor Disorders (COVADIS)) causes a heterogeneous pattern of non-transmural ischemia, which is not visible as a regional perfusion defect [81]. During a CAG (coronary angiography), obstructive CAD is ruled out, after which vasomotor tests are performed. To evaluate coronary vasospasm, ascending doses (usually 2, 20, 100, and 200 µg) of acetylcholine are given in the left coronary artery with continuous monitoring of symptoms and 12-channel ECG. An alternative to acetylcholine is ergonovine, but it is less effective, especially in women [82]. The acetylcholine test is positive for epicardial spasms if recognizable symptoms occur, accompanied by ischemic ECG changes and a  $\geq 90\%$  reduction of the coronary lumen. The acetylcholine test ends with the administration of nitroglycerin to ensure that there is complete vasorelaxation of the coronaries and that the patient is free of complaints.

Using systemic infusion of adenosine, the coronary flow reserve (CFR) is determined. This can be done by means of thermodilution or Doppler [83]. An invasively measured CFR  $< 2$  is generally used as a cut-off value for the detection of ischemia in CMD. The basis for this is the finding that CFR  $< 2$ , measured by PET, is related to a clearly worse cardiovascular prognosis [84], [85]. CFR  $> 2.5$  is considered normal. CFR values between 2 and 2.5 form a gray area.

If thermodilution is used, the index of microvascular resistance (IMR) is determined and the evaluation is done with Doppler to determine the hyperemic microvascular resistance (HMR)[86]. IMR of 25 U is generally used as cut-off, with values above 25 being diagnostic for CMD. For HMR, 2.5 mmHg/cm/s is often used as a cut-off value for the diagnosis of microvascular disease[87].

In patients with acute myocardial infarction, coronary microvascular dysfunction is responsible for the so-called 'no-reflow' phenomenon, which is associated with a worse outcome. Therefore, it is recommended that all patients undergoing an invasive test, a complete coronary vasomotor test with administration of both acetylcholine and adenosine should be performed.

PET, CMR and TTDE have been considered) for the detection of coronary vascular dysfunction [88]. With TransThoracic Doppler Echocardiography (TTDE), the Coronary Flow Velocity Reserve (CFVR) can be determined in the Left Anterior Descending coronary (LAD). The CFVR is the ratio of the peak velocity in hyperemia (using systemic adenosine) vs the peak velocity in rest in the LAD and a surrogate for CFR. In CMR (Cardiac magnetic resonance), a technique has been developed to determine the Myocardial Perfu-

sion Reserve Index (MPRI) by using a contrast medium (gadolinium), diffusing from the microvasculature into the interstitial space, perfusion signal intensity upslopes are evaluated in stress (induced with adenosine) vs. rest, the ratio being the MPRI, which is considered a surrogate for the CFR[89]. CMR is more widely available than PET, less expensive and involves no radiation Cardiac Positron Emission Tomography (PET), a radionuclide imaging technique, is considered the most reliable method using  $^{15}\text{O}$ -water,  $^{13}\text{N}$ -ammonia, or  $^{82}\text{rubidium}$  tracers [90] for accurate and reproducible quantification of regional myocardial blood flow (MBF) and CFR in the myocardium[91].[92] and correlates well with invasive assessment of CFR[93]. Despite, PET is not widely used due to some major limitations, namely, high expense, the necessity of an on-site cyclotron when using  $^{15}\text{O}$ -water and  $^{13}\text{N}$ -ammonia, and the involvement of radiation [94-96]. However, the described methods only assess CFR and the cold-pressor PET which cannot distinguish between epicardial and microvascular vasospasm. Vasospasm is the most prevalent endotype in patients with coronary vascular dysfunction, occurring in 81-97% of patients, while an abnormal CFR or microvascular resistance without vasospasms occurred in only 3-19% [97],[98].

Recently, a novel method has been validated that allows this direct quantification of absolute coronary blood flow (Q) and resistance (R) using continuous thermodilution [99-101].

## 5.6. Sudden Cardiac Death (SCD)

The anomalous coronary artery arising from the opposite sinus is related to 14-17% of all cardiac deaths among young athletes during or immediately after physical exercise [102], mostly between the ages of 10 and 30 [103]. Sudden cardiac death in older individuals is less common due to lower rate of participation in high-intensity sports [104] and is normally associated with atherosclerotic events. Sudden death has major social impact as the result of high number of years of life potentially lost [105]. The anomalous origin of left coronary artery seems to be responsible for up to 85% of cases of sudden cardiac death, which makes it more fatal. Occlusion of the left coronary artery results in a massive anterolateral and septal ischemia, followed by tachycardia/ventricular fibrillation or extensive myocardial infarction and cardiogenic shock. If the occlusion is in the proximal region of the right coronary artery, the resulting infarction occurs in the inferior region of the myocardium and is usually not fatal [106]. Transient ischemia with anomalous coronary arteries, leads to malignant arrhythmias causing SCD. The proposed mechanisms of ischemia induced SCD [107] are shown in Table 5.

**Table 4:** Types of CMD

Type (CMD)	Definition
1	in the absence of obstructive CAD and myocardial diseases
2	associates with cardiomyopathy
3	occurs in the presence of obstructive CAD
4	iatrogenic.



**Table 5:** The mechanisms of sudden cardiac death in coronary anomalies.

S.No	Mechanisms
1	acute angulation at the ostium of coronary artery and kinking
2	an abnormal slit-like opening;
3	mechanical compression of the anomalous artery during exertion
4	vasospasm of the anomalous artery

5.7. Single Coronary Artery (SCA)

This is a very rare condition, occurring in approximately 0.024% of the population in which only one CA (coronary artery) arises from the aorta and may originate either from the left or the right Valsalva sinus and can coexist with other congenital anomalies. Endothelial hyperfusion can result in the reduction of coronary blood vessels and failure of one of the two CAs (coronary arteries) to muscularize, can be a factor explaining the absence of a major coronary vessel. It may take the course of either an RCA (right coronary artery) or an LCA (left coronary artery) as in Figure 4 and divide shortly from its origin into two or three of the main coronary branches as in Figure 3. Lipton et al. [108] proposed an anatomical classification of single CA, shown in Table 6 based on the location of the ostium, anatomical distribution, and course. Table 6.

Although single CA may be compatible with a normal life expect-

tancy due to the development of collateral branches, patients are at increased risk of myocardial ischemia and SCD when a major CA branch courses between the pulmonary artery and the aorta [109], especially when the single CA originates from the right sinus. A rare case of isolated SCA with absent RCA, with LCX (left circumflex coronary artery), a large vessel which supplied also the territory of the right coronary artery (RCA) through its terminal extension, presented with unstable angina in a 56-year-old female was reported [110]. Taylor et al. Analysed 242 deceased patients with isolated congenital coronary anomalies and found that one-third of the patients suffered sudden cardiac death, and half of these were exercise-related deaths [111]. The features like acute take-off angle of the anomalous vessel, slit-like orifice, and proximal intramural course, are characteristics that can predispose to anginal symptoms and sudden death during exertion [112].

**Table 6:** Lipton's classification of single coronary artery

Originating from right cusp	Description	Originating from left cusp
RI	Solitary vessel arising from either the left or right coronary cusp, following the course of either a normal right or left coronary artery	LI
RIIA		LIIA
RIIIB		LIIB
RIIP		LIIP
RIII	Absent left coronary artery with the left anterior descending and circumflex arteries arising from the common trunk originating from right coronary cusp	

5.8. Myocardial Bridges

A myocardial bridge is defined as an atypical course of a coronary artery intramyocardially, which may result in compression of the vessel during systole (milking effect) and usually seen in the proximal and mid-segment of the LAD (left anterior descending artery). It may lead to ischemia, when characterized by a deeper (5 mm) and longer (2-3 cm) intramyocardial course, with the myocardium encircling the intramural segment acting like a sphincter [113, 114]. Myocardial bridging occurs frequently in patients with hypertrophic cardiomyopathy, with a prevalence as high as 30% [115, 116]. The major challenge is the functional assessment as it is the incidental finding of angiography or CT imaging [117] since it constitutes an anomaly or a normal variant, according to its frequency in the general population in imaging or autopsy studies [118]. Stress single-photon emission CT can detect reversible myocardial perfusion defects in those patients, with a correlation between the amount of ischemia

and degree of systolic luminal narrowing. 256-slice CT contrast-enhanced coronary angiography, a Curve multiplanar reconstruction imaging may show an intramyocardial course and shifting into myocardium of middle LAD with a typical “step down-step up” phenomenon[119]. Coronary physiological measurements during pharmacological infusion are also helpful. A Characteristic flow pattern in the bridged segment can be demonstrated by intracoronary Doppler imaging as a steep rise in the flow velocity at early diastole is followed by a sharp deceleration and subsequent plateau (“fingertip’ phenomenon”) [120]. Imaging by IVUS (intravascular ultrasound) can reveal the characteristic “half-moon” sign, an echolucent area between the bridged coronary segment and epicardial tissue that persists throughout the cardiac cycle [121].

5.9. Hypoplastic coronary artery

Hypoplastic coronary artery was first reported in 1970 and refers to congenital underdevelopment of one or more major branches with

greatly decreased luminal diameter or length.[122],[123]. Ogden et al found an incidence of 0.022% of hypoplastic proximal coronary artery as in Figure 2 in a study of 224 necropsy cases of congenital coronary artery anomalies.[124]. In living patients, the diagnosis is made by coronary angiography and in a recent analysis of 58,023 coronary angiographies performed in adult patients, coronary artery anomalies were diagnosed in 257 patients (0.44%) with congenital atresia in only 16 patients (atretic RCA in two patients; atretic left circumflex in 14) [125].

A right rudimentary coronary artery has been first described by Walter B. Whiting in 1937 [126]. The term hypoplastic right coronary artery is used in case of a short course that does not reach the crux cordis, a further feature is a narrow vessel lumen [127] and can be an incidental finding on invasive coronary angiography, cardiac CT or cardiac MRI and there have been reports of arrhythmias, myocardial ischemia, syncope or sudden cardiac death as an initial presentation [128].

## 6. Therapeutic Aspects

### 6.1. Medical therapy

Administration of Nitrates accentuate the degree of systolic narrowing in myocardial bridges and should be avoided because they may worsen the symptoms.

Logically,  $\beta$  blockers are advisable to control tachycardia related ischemia due to myocardial bridges on exertion, recommended in patients with predominantly exercise-related complaints and may be given on close follow up if there is any further episodes of chest discomfort occurs in this patient [129],[130] Nearly all ischemic episodes occurring in the morning and early afternoon are associated with increases in heart rate [131] and, presumably, are related to increases in myocardial oxygen demand [132]. Consequently,  $\beta$ -adrenergic receptor blockade with nadolol was extremely effective in preventing the morning increase in ambulatory ischemia. By contrast, nadolol therapy was actually associated with an increase in the number of ischemic episodes not associated with an increase in heart rate [133]. This increase in presumably supply-mediated episodes, which may be due in part to episodic coronary vasoconstriction, occurred primarily in the late afternoon and nighttime, suggesting that nadolol therapy may have had deleterious effects on myocardial oxygen supply during that period [134].

First-line therapy consists of a non-dihydropyridine calcium channel blocker and a short-acting nitrate to stop vasospasm episodes [135] and if insufficient, a long-acting nitrate can be added [136]. Nicorandil is an effective agent for epicardial spasms and can be added if symptoms are insufficiently controlled [137]. Nicorandil often works better than other long-acting nitrates because, in addition to its effect on nitric oxide production, it has a beneficial effect on the smooth muscle cells around the vessel wall [138]. Non-selective  $\beta$ -blockers, such as propranolol, should be avoided if there is suspected coronary artery spasm, as they can trigger spasm [139],[140],

however, nebivolol (a selective  $\beta$ -1 receptor blocker, but also has vasodilatory effects through NO production) was shown to reduce coronary vasospasm [141], [142] although not as effective as diltiazem[143]. Atenolol improves exercise capacity and anginal symptoms [144]. Carvedilol and labetalol ( $\beta$ -blockers with both  $\alpha$ -1 and  $\beta$ -adrenergic receptor antagonist properties) are also recommended for CMD due to their vasodilatory effect [145]. Calcium channel blockers are recommended because they have been shown to be effective in both epicardial spasms and CMD[146],[147]. Both non-dihydropyridines (e.g., diltiazem) and dihydropyridines (e.g., nifedipine retard) calcium antagonists can be given.

Ranolazine is a sodium channel blocker that reduces intracellular calcium in cardiomyocytes leading to improved intraventricular relaxation and microcirculation. A recent randomized trial in 81 patients showed that ranolazine improves symptoms and myocardial perfusion in patients with a CFR < 2.5 [148]. Trimetazidine, an anti-ischemic metabolic agent that improves myocardial glucose utilization through inhibition of fatty acid metabolism and improves angina and stress testing results [149]. A low dose of imipramine, a tricyclic antidepressant can be considered as a pain reliever.

Novel drugs are promising, the 'Rho kinase inhibitor' Fasudil, is effective in preventing acetylcholine-induced vasospasm [150] and other potentially effective agents include type 3 and type 5 phosphodiesterase inhibitors (cilostazol and sildenafil, respectively). In a multicenter randomized trial of vasospastic angina patients refractory to amlodipine, type 3 phosphodiesterase inhibitor (PDEI), cilostazol, reduced the anginal frequency and intensity without serious adverse effects [151]. In women with ANOCA (Angina with No Obstructive Coronary Arteries), sildenafil (a type 5 PDEI) acutely improved the CFR when it is < 2.5 (i.e., CMD) [152].

Endothelin 1 (ET-1) contributes to coronary endothelial dysfunction and its tonic inhibitory effect on myocardial perfusion is related to atherosclerosis risk factor burden [153]. Two small randomized trials of an endothelin-1 (ET-1) receptor antagonist in MVA suggested a beneficial effect [154, 155]. Currently, the Precision Medicine With Zibotentan in Microvascular Angina (PRIZE) trial [156] is investigating the effect of zibotentan, an oral endothelin A receptor-selective antagonist, on symptoms, exercise duration and myocardial blood flow in patients with microvascular angina. Dysregulation of the endothelin system is implicated in the development of CMD, and therefore zibotentan has potential as a disease-modifying therapy for CMD.

The endothelium-derived relaxing factor NO (nitric oxide) is synthesized from the amino acid L-arginine by a family of enzymes, the NO synthases, through a metabolic route, namely the L-arginine-NO pathway [157]. NO mediates vascular smooth muscle cell relaxation and inhibits platelet aggregation and adhesion and smooth muscle cell proliferation [158]. Coronary endothelial dysfunction may be a mechanism of exercise-induced myocardial ischemia in patients with effort angina and normal coronary arteriogram[159] It



has been recently suggested that an increased synthesis of asymmetric dimethylarginine, which is known to reduce the bioavailability of L-arginine for NO synthase, contributes to the impaired NO activity in these patients [160] and long term oral supplementation with L-arginine for 4 weeks preserved endothelial function in CAD (coronary artery disease) and markedly reducing LDL oxidation [161] and improve exercise tolerance [162]

In epicardial coronary spasm, high-dose aspirin (as given for pericarditis) is not recommended because the blockade of prostacyclin production, can aggravate the spasm [163]. Therefore, aspirin is not routinely given in patients with coronary spasm without obstructive CAD [164]. However, in patients with non-obstructive atherosclerosis with focal epicardial spasm at the location of coronary plaques, the use of low-dose aspirin (80–100 mg per day) is beneficial.

Since most patients (approximately 70%) with microvascular angina are women during or after menopause, it has been suggested that estrogen deficiency plays a pathogenic role in this disorder. Estrogen receptors are widely expressed in the cardiovascular system [165] and the estrogen inhibits and nicotine enhances the expression of Rho-kinase in human coronary VSMC (vascular smooth muscle cell) in vitro and that Rho-kinase is up-regulated in coronary VSMC in a porcine model of mental stress in vivo. These results may explain, at least in part, why microvascular angina is frequent in women who are post-menopausal and/or under mental stress condition. Short-term supplementation with 17-estradiol reduced the frequency of angina episodes in post-menopausal women with the disorder [166]. However, to date, there is no direct evidence that estrogen supplementation causes sustained improvement in coronary microvascular responses in those patients. Women with menopause have higher levels of anxiety or stress than those with coronary artery disease [167]. Postmenopausal women also have many vascular risk factors (e.g., diabetes mellitus, obesity, hypertension, mental stress), which cluster more frequently in women than in men.

Serotonin plasma levels were significantly higher in patients with CMD [168], the selective serotonin reuptake inhibitors (SSRIs) exhibit endothelium protective properties, reducing inflammation and improving calcium/nitric oxide-mediated vasodilatation and sertraline therapy significantly reduced CRP and IL-6 levels [169].

Non-medical anti-anginal therapy such as a Transcutaneous Electrical Nerve Stimulation (TENS) can be considered for severe refractory symptoms [170], however, studies report varying the results of this therapy on angina pectoris in CMD patients [171].

## 6.2. Surgical interventions

Coronary artery bypass grafting, preferably using the internal mammary artery is the surgical treatment of choice for coronary artery atresia [172]. Coronary angioplasty with placement of stent is the treatment of choice for myocardial bridges if convincing evidence of myocardial ischemia exists either in rest ECG, exercise stress testing or myocardial perfusion imaging in selected patients [173],[174]

but the results have been mixed. Unroofing the myocardial bridges [175] has been reported to reduce the incidence of ischemia, sudden death and arrhythmia especially in those with hypertrophic cardiomyopathy with documented ischemia [176].

## 6.3. Close follow up

Close follow up is necessary since there is a high propensity of the coronary anomalies [177, 178]. especially those with the anomalous vessel that passes between the two great arteries, to develop myocardial ischemia and sudden cardiac death, particularly in young and otherwise healthy individuals. Documentation of precise ischemic risk for some of these anomalies using conventional exercise stress testing or intravascular Doppler flow studies is poorly predictive and may fail to detect significant anatomic abnormalities. A normal exercise stress testing has been reported in patients who subsequently died suddenly [179],[180] and had an anomalous coronary artery and so it is not a reliable screening test to exclude congenital coronary anomalies in large athletic population [181]. Similarly, intracoronary ultrasound (IVUS) may not be indicated since the anomalous vessel is highly tortuous in this patient as in Figure 8.

Thus it is possible that certain myocardial bridges, especially those of long length that courses deeply within the myocardium may also be responsible for sudden unexpected cardiac death following tachycardia related ischemia. Patients with myocardial bridging of coronaries should avoid strenuous physical activity since delayed diastolic relaxation in the bridged segment in humans has been reported.

## 7. Case Analysis

A 46 year old, previously asymptomatic diabetic woman having the coronary artery anomaly, "Isolated left single coronary artery with left circumflex continuing to form the Right coronary artery with myocardial looping" based on coronary arteriography as in Figures 4 to 8 and CT Angiography as in Figure 1 [182]. presented with sudden onset of exertional chest discomfort. Her symptoms relieved spontaneously and asymptomatic on further follow up of 15 years with routine normal activities and living up to 61 years at present. Coronary Magnetic Resonance Angiography shown in Figures 2 and 3 revealed Isolated left main coronary artery trifurcates into left anterior descending, ramus intermedius and left circumflex arteries. Angina pectoris [183] and myocardial lactate production have been documented in patients with single coronary arteries where coronary atherosclerosis [184, 185] or an anomalous coronary artery passage was absent. The sudden onset of exertional chest discomfort may be due to tachycardia related episodic ischemia as shown in Exercise ECG 3, caused by myocardial looping of proximal portion of right coronary artery as in Figure 1 [186]. The ischemia is not obligatory since there is no documented evidence as per the established criteria for myocardial ischemia (horizontal or down-sloping ST-segment depression  $\geq 1$  mm at 60–80 ms after the J point.) either in rest or exercise ECGs 1 to 3 and exercise ECG 4R1 and R2 [187]. Exercise ECGs with up-sloping ST-segment depressions are typically

reported as an 'equivocal' test. Usually, the maximum percent reduction in diameter during systole is 56 % in myocardial bridging and the range is 30 to 100 % [188]. Systolic myocardial contraction does not limit coronary flow at heart rates less than 160 bpm or unless coronary compression extends to early diastole [189] and in this patient, the coronary flow get reduced when the heart rate increases > 160 bpm at peak exercise in stage 3 Bruce protocol and produced anginal episodes.

## 8. Outcome

Several anatomical studies have reported a protective effect of myocardial bridging that may involve protection from systolic wall stress. Myocardial bridges may slightly increase the chances of proximal coronary atherosclerosis while protecting the bridged segment and the distal artery and the overall frequency of myocardial infarction is same in patients with and without myocardial bridges [190]. Even though the mechanism of myocardial ischemia is speculative, most adverse outcomes appear to result from decreased myocardial perfusion [191],[192]. This patient is remaining healthy and still living as aged 61 years without any medications and interventions.

## 9. Exercise Programme

Ischemia is unlikely to occur every time when the patient exercises [193] and the presence of additional factors such as volume status and type of physical activity (isotonic, e.g., cycling or running vs. isometric, e.g., weight-lifting [194, 195] may also contribute. SCDs commonly occur in patients participating the dynamic sports and the hemodynamic relevance depends directly on the supplied viable myocardial mass in the downstream of the stenosis. A two-tier concept for the pathomechanisms of ischemia is proposed [196] and in this concept, the occurrence of ischemia is based on the extent of a fixed (anatomic high-risk features of slit-like ostium and proximal narrowing (also referred to as hypoplasia) and a dynamic (acute take-off angle, intramural course with the elliptic vessel shape) component.

Acute take-off angle (below 45°), defined as an axial course of the proximal segment tangential to the great vessel circumference [197] and kinking of the anomalous coronary artery during exercise, i.e., decrease of the acute take-off angle and consequently increased narrowing at the ostium, was proposed as a contributing ischemia-inducing mechanisms [198, 199]. Intramural course is a threatening feature of hemodynamic relevance [200, 201] as shown by several studies and the length of the intramural segment is associated with an increased risk for ischemia [202, 203]. In addition, an elliptic proximal vessel shape (defined as height/width ratio of >1.3) [204] is frequent within the intramural segment, and the deformation (also called lateral compression), dependent from the cardiac phase, i.e., more pronounced during systole than diastole [205] has been shown to increase during physical activity with augmented great vessel wall stress [206]. The reduction of the cross-sectional area creates flow restrictions and the Fractional flow reserve (FFR, defined

as the hyperemic mean distal coronary artery pressure divided by the simultaneous recorded mean aortic pressure) [207] was used to assess the hemodynamic relevance of anomalous coronaries in multiple studies and the dynamic component cannot be sufficiently reproduced using pharmacological stress with vasodilators.

The ideal stress test should be able to assess both dynamic and fixed components and has to be strenuous enough to provoke ischemic symptoms. Maximal exercise load is crucial and should aim for maximal or supramaximal stress (100% of predicted maximal heart rate or above, estimated with the formula of 220-age). Unfortunately, most performed stress tests were satisfied with 85% of the maximal heart rate [208] and it has a low reliability for correlation with clinical symptoms and prognosis [209].

"SAD"-test [210] is an invasive pharmacologic stress testing, introduced by Angelini et al with rapid infusion of 500 ml saline, dobutamine stepwise infusion up to 40 µg/kg/min and in addition 0.5 mg atropine if the heart rate is below 140 bpm at the end of the dobutamine infusion and this stress protocol is the closest equivalent to vigorous exercise. A more aggressive approach with steady infusion of saline during the whole invasive procedure (usually more than 1500 ml of saline to prevent a preload decrease) and attempts to reach 100% of the maximal heart rate, i.e., using atropine in addition to the ongoing dobutamine infusion to simulate vigorous physical exercise at the upper limit. The dobutamine and volume challenge is, of course, not practicable for every patient but should be aimed for in order to simulate maximal physical exercise and obtain conclusive results even in absence of ischemia (i.e., true-negative results).

The patients also stressed the importance of a minimum of stimuli (for example audio: the acoustics as well as the volume, preferably no music or loud voices) and pressure (for example setting goals with time limits) since it can trigger symptoms. Furthermore, they expressed the need for a slow start-up. Research has confirmed the importance to do a thorough warming-up (minimal 10 min on 50–60% of maximum intensity) to avoid "warm-up angina" [211, 212].

## 10. Conclusion

The point of importance from this case study is junctional (J point) ST depression with rapid up sloping of ST segment at peak exercise as shown in Exercise ECG 3 with rapid normalization in the recovery phase as shown in Exercise ECG 4 R1, R2 in Treadmill Testing may be due to episodic ischemia related to tachycardia with the heart rate of more than 160 bpm is significant and warrants further cardiac evaluation [213].

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