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An Overview on Wellens Syndrome

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Abstract

Wellens syndrome is a pre-infarction stage of critical stenosis in the proximal left anterior descending (LAD) coronary artery, first described in the early 1980s. It is characterized by specific electrocardiographic (ECG) patterns in patients who are often pain-free at the time of presentation. These patterns include deeply inverted or biphasic T waves in the anterior precordial leads (V2–V3), with little or no elevation of cardiac enzymes. Despite the absence of acute ST-segment elevation, the syndrome signifies a very high risk of imminent large anterior wall myocardial infarction if left untreated. Recognition of Wellens syndrome is clinically important because patients may appear stable, but inappropriate management—such as stress testing—can precipitate acute myocardial infarction or sudden cardiac death. Early identification on ECG, combined with urgent coronary angiography and revascularization, can be lifesaving.

Keywords: Wellens syndrome; Pre-infarction angina; Left anterior descending artery (LAD); Biphasic T wave; Inverted T wave; Acute coronary syndrome (ACS); Myocardial infarction; Electrocardiography (ECG); Coronary stenosis

Introduction:

Coronary heart disease is the leading cause of death and morbidity in developed countries. Although deaths from this condition have gradually decreased over the past few decades in European countries, it still accounts for about one-third of deaths in people over 35 years old. The American Heart Association (AHA) reported that 15.5 million people ≥20 years old in the United States have coronary heart disease. At the same time, the prevalence increases along with age for both women and men, and myocardial infarction occurs approximately every 42 seconds. (**1)**

Wellens syndrome (WS) was first described by de Zwaan et al. in a subgroup of patients with unstable angina who had inverted anterior on their electrocardiogram findings (ECG). The classification of WS can be divided into type A marked by biphasic T- wave inversions in leads V2 and V3, often including leads V1, V4, V5, and V6 and type B, which is characterized by deep, symmetrical T-waves in leads V2 and V3 during the pain-free period. These findings are associated with stenosis of the anterior descending artery. However new studies have described (WS) with lesion in right coronary artery and left circumflex artery or it could be associated with multivessel diseases **(2)**

Deeply inverted T waves in leads V2 and V3 (may also be seen in leads V1, V4, V5, and V6) OR biphasic T waves (with initial positivity and terminal negativity) in V2 and V3

PLUS

- Isoelectric or minimally elevated ST segment, less than 1 mm.
- Preservation of precordial R-wave progression AND no precordial Q waves (in other words, no signs of old anterior wall infarct)
- Recent history of angina

- ECG pattern present in a pain-free state
- Normal or slightly elevated cardiac markers
- Two patterns of T waves can be seen in Wellens syndrome. Type- A T waves are biphasic, with initial positivity and terminal negativity. These T wave findings are present in approximately 25% of cases. Type-B T waves are deeply and symmetrically inverted. These findings are present in approximately 75% of cases. The 2 types of T waves found in Wellens syndrome exist on a spectrum of disease with type-A T waves evolving into type-B T waves. The T-wave abnormalities may be persistent, remaining in place for hours to weeks, even when the patient is pain-free **(3).**

Wellens syndrome is not always an acute process. It can develop over days to weeks. The ECG pattern often develops when the patient is not experiencing chest pain. When the patient does experience chest pain, the ST segment and T-wave pattern can appear to normalize into hyper acute upright T waves (so-called ―pseudo-normalization‖) or even develop into ST-segment elevations.

Cardiac biomarkers including troponin may be falsely reassuring in patients with Wellens syndrome as they frequently result within normal limits. In one prospective study, only 12% of patients with Wellens' pattern on ECG had elevated cardiac enzymes, and these elevations were less than twice the upper limit of normal.

In view of prevalence, Analysis of 274 consecutive patients presenting with NSTEMI who underwent coronary angiography categorized patients into a Wellens group and other types of acute coronary syndrome. 8.8% (24 patients) had Wellens syndrome. 16 patients had LAD culprit, 2 patients had non lad culprit and 6 had non obstructive lesion **(4)**

Several case reports were published over the past few years describing typical and atypical presentations. Some described typical cases of young male patients **(5).**

Also in another case unlike the classic Wellens syndrome, which needs aggressive coronary intervention, the patient showed favorable prognosis with conservative medical therapy **(6)**

Recently, a larger scale study was conducted in 2022, highlighting a Wellens syndrome incidence of 5.7% among 3528 ACS patients. NSTEMI was more frequently encountered, and early coronary angiography was more prominent among Wellens syndrome patients. The study found that Wellens syndrome was not associated with poor prognosis, except in the presence of specific risk factors such as diabetes, advance age and chronic kidney disease **(7)**

Etiology for WS was coronary artery diseases such as atherosclerotic plaque, coronary artery vasospasm, hypoxia, and increased cardiac demand. Two studies in hospitalized unstable angina, WS can be found on 14% - 18% ECG findings, and 75% of WS patients who did not undergo myocardial revascularization had an extensive anterior myocardial infarction within the first few weeks of treatment, indicating the importance of early diagnosis of this syndrome**(7)**

Definition and Risk Factors

WS is a clinical condition characterized by left descending proximal anterior artery stenosis and massive myocardial infarction on the anterior wall, however recent studies have described lesions in other vessels. **(8**)

Most cases of WS involved proximal segment with the most common ECG finding was type B marked by precordial T wave inversion in V1-V5 (76%) and type A in V2-V3 (24%).**(9)**

Risk factors of WS include a family history of premature coronary heart disease, type II diabetes mellitus, metabolic syndrome, hypertension, smoking, hyperlipidemia, work stress, advanced age (55 ± 9 years), HIV-related cases, history of early coronary disease as well as in patients without cardiovascular risk factors**.(10)**

The pathophysiology of Wellens syndrome:

Wellens syndrome is a pre-infarction condition that typically signifies critical stenosis of the proximal

left anterior descending (LAD) artery, placing patients at high risk of an impending anterior wall myocardial infarction **(11).**

However, recent evidence suggests that Wellens-like ECG changes can occur due to ischemia in other coronary territories, though LAD involvement remains the most common etiology **(12).**

The underlying mechanisms involve transient ischemia, reperfusion injury, and characteristic electrocardiographic (ECG) changes.

1. Proximal LAD Artery Stenosis and Myocardial Ischemia

Classic Wellens syndrome is caused by a high-grade stenosis or subtotal occlusion of the proximal LAD artery, leading to severe ischemia in the anteroseptal and anterior wall regions**(12).**

However, similar ECG changes have been observed in patients with occlusion or severe stenosis in other coronary arteries, such as the left circumflex artery (LCx) or right coronary artery (RCA), particularly when they supply the anterior wall through collateral circulation **(13).**

2. Transient Ischemia and Reperfusion Phenomenon

The ECG changes in Wellens syndrome result from episodes of transient ischemia followed by spontaneous reperfusion **(14).**

During ischemia: The affected myocardium experiences severe oxygen deprivation, leading to subendocardial injury.

During reperfusion: Partial restoration of blood flow occurs, leading to repolarization abnormalities, which manifest as the characteristic biphasic or deeply inverted T waves in leads V2–V3 **(15).**

3. Electrophysiological Mechanisms of T-Wave Changes

The biphasic or deeply inverted T waves are caused by ischemia-induced changes in myocardial repolarization **(12).**

This is attributed to:

Alterations in potassium currents, particularly affecting delayed rectifier (IKr) and inward rectifier (IK1) potassium channels.

Differences in repolarization between the subepicardium and sub endocardium, creating the observed T-wave morphology **(16).**

4. Wellens-like ECG Changes Not Always Due to LAD Disease

Although Wellens syndrome is classically associated with proximal LAD stenosis, several reports suggest that similar ECG findings can be seen in patients with stenosis in other arteries, particularly when ischemia affects the anteroseptal or anterior wall **(13).** Conditions that can mimic Wellens syndrome include:

- Severe LCx or RCA stenosis with collateral supply to the LAD territory.
- Multi-vessel coronary artery disease (CAD).
- Takotsubo cardiomyopathy, which can cause transient LAD ischemia-like patterns.
  - Spontaneous coronary artery dissection (SCAD), affecting any coronary artery.

5. Minimal or No Biomarker Elevation in Early Stages

Unlike acute myocardial infarction, early stages of Wellens syndrome may show only mild or no elevation of cardiac biomarkers, such as troponin, since irreversible myocardial necrosis has not yet occurred **(14).** However, progression to complete LAD or other artery occlusion leads to significant biomarker release.

6. Risk of Progression to Extensive Myocardial Infarction

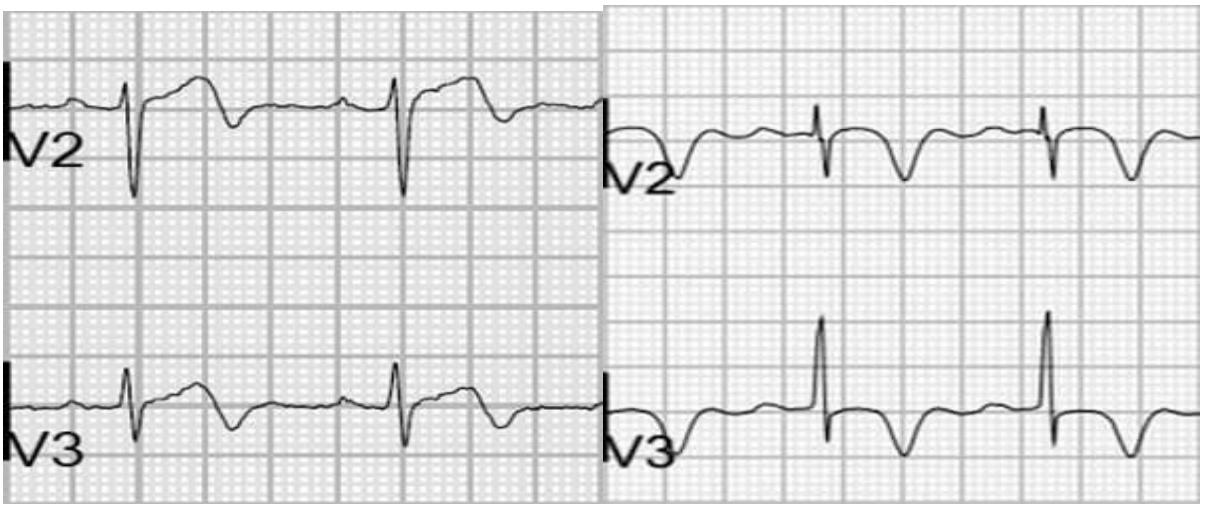
Without urgent intervention, the stenotic coronary artery may fully occlude, leading to an extensive anterior wall ST-elevation myocardial infarction (STEMI) **(11).** Immediate coronary angiography and revascularization are essential to prevent myocardial necrosis and improve outcomes.

Diagnosis

The diagnosis of WS depends on clinical history, ECG changes, and cardiac biomarkers. The clinical manifestation of WS consistent with an acute coronary syndrome, including chest pain or tightness or pressure-like usually induced by physical activity, relieved by rest, may radiate to the neck, jaw, or shoulder. Chest pain as a sign of myocardial ischemia was caused by total or near-total obstruction of LAD. Patient usually presented during a pain-free period at an emergency department**. (7)**

Physical examination revealed proto diastolic murmur on the third intercostal space above the midline of the left clavicle, which may be due to turbulence of direct distal blood flow to the stenotic segment, known as a Dock's murmur. The diagnosis can be confirmed by coronary angiotomography in a hemodynamically stable patient or by doubt on the initial examination. This is the most accurate and reliable noninvasive modality to exclude significant coronary artery stenosis**. (17)**

The diagnostic criteria for WS are as follows: deep inverted T waves in leads V2 and V3 (also seen in leads V1, V4, V5, and V6) or biphasic T waves (with initial positivity and negative terminals) in V2 and V3, absence of Q waves without loss of precordial R waves, no significant ST- segment elevation (< 1 mm), normal or minimally increased cardiac markers, history of chest pain and T wave changes (biphasic or inverted) in the precordial leads during the pain-free period, Inverted or biphasic T-waves in the precordial leads were caused by repolarization abnormalities due to reperfusion injury and myocardial edema. (**9).**



Type (A) Type (B)

Figure (1): ECG examples of wellens syndrome types **(18)**

Serial ECG and cardiac enzyme laboratory should be performed. Echocardiography can be beneficial in patients with atypical chest pain because it can detect any cardiac abnormality before the rise of serum troponin. Based on current guidelines, the stress test should be performed within 72 hours or admission to chest pain units for stress testing consideration. **(1)**

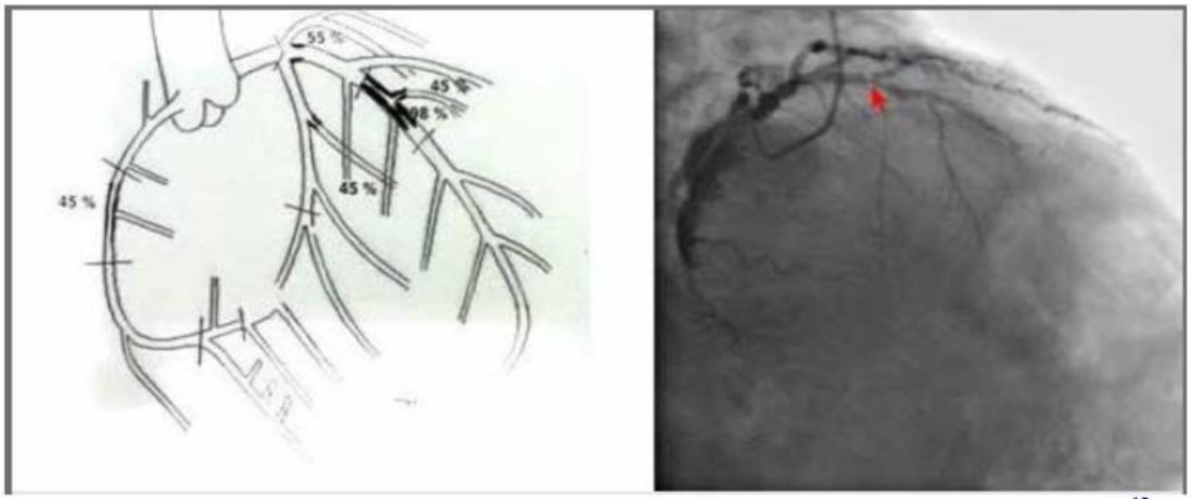


Figure (2): Coronary Angiographic Findings with Narrowing of the Medial LAD Proximal LAD. **(9)**

The differential diagnosis of precordial T-wave inversion includes pulmonary embolism, cerebral hemorrhage, left ventricular hypertrophy, cocaine or morphine-induced coronary vasospasm (pseudo-Wellens syndrome), chronic pulmonary thromboembolic hypertension, interruption or transient left bundle branch block, or Wolff-Parkinson-White pattern (WPW), persistent juvenile T wave pattern, late-stage pericarditis, digitalis effects, and Takotsubo cardiomyopathy.**(1)**

Treatment:

WS is the pre-infarct stage of acute coronary syndrome; therefore, recognizing this syndrome can be a life-saving diagnosis. T-wave changes in WS are usually observed in asymptomatic patients. Although these patients may initially respond well to medical management, they ultimately have poor outcomes with conservative therapy and require a revascularization strategy**. (19)**

The early management of WS is to assess airway patency, maintenance of breathing and circulation, oxygen supplementation and monitoring for a vital sign, intravenous access, administration of aspirin, clopidogrel, nitrate, beta- blocker, and morphine if needed, serial ECG examination, laboratory examination including cardiac marker (troponin I or T) and chest X-ray. **(9)**

Because the definitive treatment for WS is procedural or interventional, as soon as the diagnosis of WS is confirmed, consult an interventional cardiologist, and coronary angiography should be performed. This is beneficial for evaluating further management, such as angioplasty or coronary artery bypass procedures. Symptomatic patients should be monitored in the intensive care unit, and cardiac catheterization should be performed in an emergency setting. Stress test which can induce acute myocardial infarction and sudden death is contraindicated in WS patients who had severe stenosis of LAD. **(17)**

Delayed coronary revascularization can also lead to left ventricular dysfunction and death due to extensive acute myocardial infarction of the anterior wall. Treatment with multiple antiplatelet (acetylsalicylic acid and clopidogrel), thrombolysis, blood pressure, glucose control, and statin therapy alone did not reduce complication rates and mortality. Therefore, it requires holistic management, including medical and intervention management. According to the recent meta-analysis, ticagrelor is associated with a higher risk of significant bleeding than clopidogrel in patients with acute coronary syndrome in East Asia. **(7)**

Subsequent studies on WS with a follow-up period for 18 months showed that the mortality rate was very high in conservatively treated patients compared to patients treated with cardiac catheterization (26.67% vs. 0.88%). All invasive procedures such as cardiac catheterization should be considered during the 2019 coronavirus disease (COVID-19) pandemic. Based on the patient's risk, conservative therapy may be sufficient for non-ST-segment elevation myocardial infarction (NSTEMI) patients with COVID-19. WS patients with COVID-19 and stable hemodynamic are recommended to be treated conservatively in an isolated hospital ward. Several reports

show an association between COVID-19 infection and cardiovascular complications, including myocardial injury, myocarditis, deep vein thrombosis (DVT), and pulmonary embolism (PE).**(18)**

Based on the Indonesian Heart Association recommendation, conservative care in isolated hospital wards should be considered if the WS patients are positive for COVID-19 and have stable hemodynamic to reduce the risk of transmission of COVID-19, especially when special standard facilities are not available. These recommendations align with Chinese Society of Cardiology guidelines, which recommend that NSTEMI high-risk patients be hospitalized and treated conservatively. **(9)**

The American College of Cardiology suggests that in patients with stable NSTEMI, conservative therapy may be sufficient based on the patient's risk. **(18)**

WS is a clinical condition with significant stenosis of the proximal LAD artery, however other vessels were detected to cause this syndrome marked by inverted T waves in precordial leads and usually occurred in a pain-free period **(7)**

WS diagnosis can be confirmed by WS diagnostic criteria derived from clinical history, ECG changes, and cardiac biomarkers. Early diagnosis leads to early referral to designated hospital, management and intervention, so mortality and morbidity rates can be reduced**. (19)**

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