Non-Q-Wave

Myocardial Infarction: Comprehensive Analysis of Electrocardiogram and Pathological Correlation

Pathological Correlation
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ABSTRACT

Non–Q-Wave Myocardial Infarction (NQwMI) has been defined as an Acute Myocardial Infarction (AMI) without a new onset deep Q wave on the Electrocardiogram (ECG) after day/days of evolution. Correlations between pathophysiology and ECG findings in the NQwMI not yet well understood and the culprit lesion after NQwMI has not been well characterized. Also, there is no consensus according to the clinical usefulness of the Qw and NQw Myocardial infarction definition. The anatomopathological concept of infarction is usually related to necrosis and it results paradoxical to consider this widely known clinical entity as a myocardial infarction when absence of ECG evidence of necrosis is observed. One of the proposed explanations to this ECG phenomenon is that in fact there is an important coronary obstruction that compromises myocardial viability but its natural history is modified by endogenous mechanisms such as tissue plasminogen activator, oxygen reactive species diminishment via superoxide dismutase, cessation of vasospasm through adenosine production and other molecular mechanisms happening before two hours of initiated the coronary flow obstruction. These are is the main discussion topics in this review article aiming to clarify why a NQwMI is in fact considered an infarction of myocardial tissue without ECG evidence of inert myocardium not capable to depolarize and if its clinical differentiation with Untable Angina represents further therapeutic implications or not.

Keywords: Non-Q-Wave Myocardial Infarction, ischemia, necrosis, electrocardiogram.

INTRODUCTION

Since the invention of electrocardiogram (ECG or EKG) its significance in the diagnosis of acute ischemic disease, chronic ischemic disease and its contribution to cardiology has been no less than remarkable. Typically and from a clinical view, Acute Coronary Syndromes (ACS's) have been described as any constellation of signs or symptoms suggestive of myocardial ischemia or necrosis, though, its final diagnosis according the ACS's nomenclature as an ST-Elevation Myocardial Infarction (STEMI), No ST-Elevation Myocardial Infarction (NSTEMI), Q-Wave Myocardial Infarction (QwMI), Non-Q-Wave Myocardial Infarction (NQwMI) or Unstable Angina (UA), also requires the determination of cardiac biomarkers and undoubtedly ECG findings.[1]

The pathophysiology of ACS's in most cases correlates with the clinical outcomes, biochemical findings (cardiac biomarkers) and electrocardiographic patterns being the severity of coronary artery obstruction and oxygen demands by myocardium main factors determining presence or absence of cardiac enzymes and ECG patterns from which Q waves are our main concern in this chapter.

Electric activity in the myocardium is registered in the ECG describing positive deflections when the depolarization potential orientates positive charges to the recording electrode (approaches to it) and negative deflections when the depolarization potential orientates negative charges to the recording electrode and gets away from it. Before analyzing pathophysiology and the electrocardio-

gram patterns of Non-Q-Wave Myocardial Infarction we shall overview basic concepts on electrophysiology and normal ECG.

The abnormal Q wave is the cornerstone of the myocardial infarction diagnosis after several days of the ischemic event. Q waves are the first negative deflection in a normal ECG and it is given due to septal depolarization taking place after atrial depolarization and prior ventricular depolarization. Q waves' amplitude in a normal ECG must be less than 25% of R wave in I and II bipolar derivations and less than 15% of R wave in V5 and V6 cardiac derivations, hence, its length should not be greater than 0.02 seconds[2].

Nonetheless, The Joint European Society of Cardiology/ American College of Cardiology Committee for the Redefinition of Myocardial Infarction considered in its ECG criteria for Myocardial Infarction that any Q-wave in leads V1 through V3, Q-wave ≥30 milliseconds in leads II, III, aVL, V4, V5 or V6, and be ≥1 millimeters in depth are abnormal and strongly suggestive of myocardial necrosis.

Findings in the ECG suggestive of ischemia and necrosis are ST elevation/depression and deep Q waves, respectively. The presence of a deep abnormal Q wave in the ECG is evidence of necrotic areas and an inert myocardium which is not capable to depolarize.

Non–Q-Wave Myocardial Infarction has been defined as an AMI without a new onset deep Q wave on the ECG after day/days of evolution. Correlations between pathophysiology and ECG findings in the Non-Q-Wave Myocardial Infarction not yet well understood and the culprit lesion after NQwMI has not been well characterized. Also, there is no consensus according to the clinical usefulness of the Qw and NQw Myocardial infarction[3].

The anatomopathological concept of infarction is usually related to necrosis and it results paradoxical to consider this widely known clinical and biochemical entity as a myocardial infarction when absence of ECG evidence of necrosis is observed.

Some authors considered that presence or absence of deep Q waves is determined by necrosis extension being the small lesions undetectable for the 12-lead ECG but extensive enough to cause biochemical changes such as cardiac enzyme elevations; others consider localization of necrosis as the main determinant of presence/absence of deep Q waves being only patients with transmural lesions those who exhibited important changes in the Q wave.

Nevertheless, the pathologic basis of Q wave and Non-Q-Wave AMI have been recently studied and compared through magnetic resonance imaging obtaining interesting results that help to elucidate the correspondences among clinical, biochemical and ECG findings of this uncommon presentation of the ACS's.

These are is the main discussion topics in this review article aiming to clarify why a NQwMI is in fact considered an infarction of myocardial tissue without ECG evidence of inert myocardium not capable to depolarize and if its clinical differentiation with UA represents further therapeutic implications or not.

BASIC CONCEPTS OF ELECTROCARDIOGRAM

Since the invention of the string galvanometer by Willem Einthoven in 1901 the registering of the electrical activity of the heart has enormously aid physicians diagnosing medical conditions not only within cardiology but medicine itself.

When cardiac cycle begins, sinoatrial (SA) node activates and cells depolarization initiates the action potential (electrical stream) which spreads throughout the conduction system of the heart passing by auriculoventricular (AV) node, bundle of His, branches of His and Purkinge fibers activating myocardium from endocardium to epicardium and producing systole then, this is immediately followed by cells repolarization and diastole[4].

This electrical activity of the heart not only occurs within it but also propagates throughout pericardium, the chest and body surface being detectable and registered by the ECG leads. As definition, the graphic registry of the electrical activity of the heart through the collocation of electrodes on the body surface able to detect differences in electric potentials is known as electrocardiogram[5].

Electrophysiological processes behind the normal electrocardiogram

Each positive or negative deflection in the ECG paper corresponds with voltage changes due to ions dynamics through the membrane of the myocardial cell.

Myocites have a transmembrane potential of -80 to -90 mV at rest being negatively charged in the inside (cytoplasm) with predominant positive charges in the outside (extracellular space). Plasmatic membrane works as a semi permeable boundary which controls the diffusion of a number of ions including, sodium, potassium, calcium and chloride. The exchange of these ions is allowed by ion channels located within the membrane and activated in response to voltage changes or via receptor linkage.

Myocardial cells undergo through an electrophysiological process given its capacity of excitability which can be summarized in 5 phases (Figure 1). In Phase 0, in response to the electrical stimuli of the SA node there is a rapid enhancement in sodium conductance in the myocardial cell and its transmembrane potential abruptly changes from -85 mV to 20 mV due to a transient increase in fast sodium channel conductance.

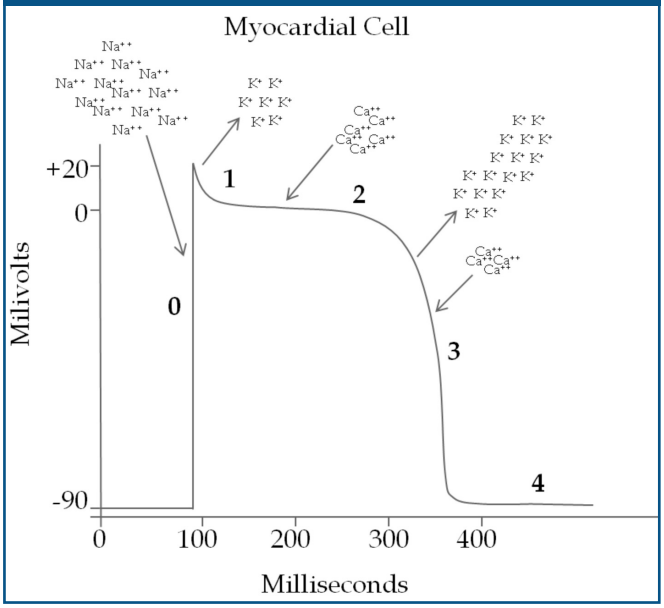
In Phase 1, voltage-dependant potassium channels opens and initiates repolarization, potassium ions goes out the myocardial cell following its gradient of concentration. Phase 2 is a plateau in the transmembrane potential due to a balance between inward-going calcium current and outward potassium current. The inward current of calcium is due to long-lasting calcium channels that open up when the membrane potential depolarizes to about –40 mV.

In Phase 3, complete repolarization is reached due to an enhancement in potassium conductance and a time depen-

dant decrease in calcium conductivity. Finally in Phase 4 myocardial cell restores its initial transmembrane potential and goes into a period in which it cannot be depolarize again until recovers its excitability properties (resting state).

This physiological process takes place in ventricular cells each time they contract and also in automated cells with small variations in transmembrane potentials and ions conductance.

Figure 1. The normal action potential of ventricular cells and ions inward/outward currents.



ELECTROCARDIOGRAM LEADS

The standard 12-Lead ECG comprises of 3 bipolar leads, 3 amplified monopole leads and 6 precordial leads in specific cases a 16-Lead ECG might be necessary. (Table 1)

Table 1. Location of Electrodes in a 12-Lead Electrocardiogram

Lead Type	Positive Input	Negative Input
Standard Limb Leads		
I	Left arm	Right arm
II	Left leg	Right arm
III	Left leg	Left arm
Amplified Leads		
aVR	Right arm	Left arm plus left leg
aVL	Left arm	Right arm plus left leg
aVF	Left leg	Left arm plus left arm
Precordial Leads		
V_1	Right sternal margin, fourth intercostal space	Wilson central terminal
V_2	Left sternal margin, fourth intercostal space	Wilson central terminal
V_3	Midway between V_2 and V_4	Wilson central terminal
V_4	Left mid-clavicular line, fifth intercostal space	Wilson central terminal
$V_{5\,\beta}$	Left anterior axillary line	Wilson central terminal
$V_{6\,\beta}$	Left mid-axillary line	Wilson central terminal
$V_{7\alpha,\,\beta}$	Posterior axillary line	Wilson central terminal
$V_{8\,\alpha,\,\beta}$	Posterior scapular line	Wilson central terminal
$V_{9\,\alpha,\,\beta}$	Left border of spine	Wilson central terminal

α: Non commonly used leads in clinical practice. Specific cases needed.

β: Leads V5 to V9 are taken in the same horizontal plane as V4.

The normal electrocardiogram: when a q wave is not normal?

Before continuing we considered necessary to recognize amplitude and duration of waves, intervals and segments in the normal ECG. P waves in the normal ECG represents the activation of SA node, depolarization of the right atrium, interatrial septum and left atrium and its duration is normally less than 120 milliseconds. The amplitude in the bipolar leads is normally less than 0.25 mV and the terminal negative deflection in the right precordial lead (V1) is normally less than 0.1 mV in depth.

Atrial repolarization is not usually seen in a normal ECG due to its low voltage and the incoming QRS complex of much higher amplitude. Nonetheless, it may be observed as a low-amplitude negative wave during atrioventricular block.

Immediately after P wave, starts PR segment representing a physiological delay when the action potential undergoes from atrium to ventricles going through AV node. This segment is described as an isoelectric line connecting the end of P wave and the beginning of QRS complex; it appears isoelectric because the potentials generated by these structures are too small to produce detectable voltages on the body surface. By the other hand, PR interval includes P wave from its beginning and ends with the onset of QRS complex; normal PR interval measures 120 to 200 milliseconds in duration.

The QRS complex is the conjunction of three waves (all three no always seen in each lead) that represents electric activity during ventricular depolarization. The resultant negative or positive deflection is defined by the direction of the depolarization vector and the lead "registering" that vector.

If the vector aims (approaches) to the registering lead, then a positive deflection shall be described in the ECG, opposite, if the vector does not aim to the registering lead and gets away from it then a negative deflection shall be seen in the ECG paper[6].

Q wave is the first negative deflection in the normal ECG and represents interventricular septum depolarization. When this septum depolarizes it describes the first vector of QRS complex which goes from left to right and anteriorly. R and S waves represent the second vector of depolarization which goes from right to left and anteriorly and then activates contraction of left and right ventricles; R wave is described as the second positive deflection in normal ECG (P wave is the first positive deflection) and S wave is the second negative deflection.

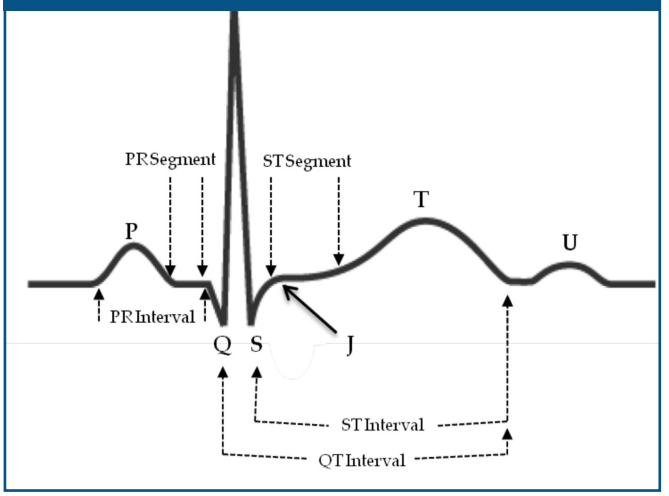
In the normal ECG (with normal cardiac axis) the R waves describe an ascending progression in amplitude from V1 to V4 and then it diminishes from V4 to V6; the inverse pattern is seen in S wave from V1 to V6. The upper nor-

mal value for QRS duration is given as shorter than 120 milliseconds.[7]

According to Vélez D., a normal Q wave must have less than 0.02 seconds (duration) and less than 3 millimeters in the ECG paper (amplitude) in leads I, aVL, V5 and V6. Thus, it must be less than 25% of R wave in leads I and II and less than 15% of R wave in leads V5 and V6.[2]

Also in a 2000 Euro-American consensus (The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction) the ECG criteria defining a Myocardial Infarction was "any Q-wave in leads V1 through V3, Q-wave ≥30 msec in leads II, III, aVL, V4, V5 or V6 (the Q-wave changes must be present in any two continuous leads), and be ≥1 mm in depth"[8].

Figure 2. The normal Electrocardiogram



The onset of ST segment and T Wave is the J point which is normally at or near the isoelectric baseline of ECG. ST segment and T Wave represent the repolarization process of both ventricles. The normal ST segment begins as an slowly ascending wave and gradually leads to the T wave usually seen as positive deflections in leads I, II, aVL, aVF and left precordial derivations. The normal amplitude an ST segment should not be more than 0,33mV, and it is usually seen in men ages 18 to 29 years[7].

Ischemia, injury and infarction

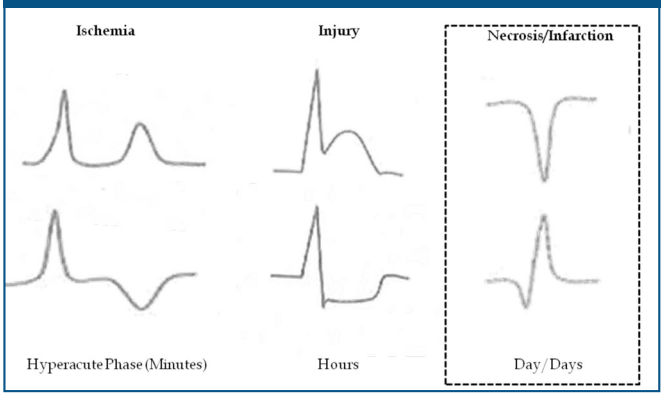
The ECG is the foundation stone in the diagnosis of acute coronary syndromes and chronic ischemic disease since early 20th century. This diagnostic tool helps the clinician to identify reversibility (ischemia, injury or necrosis), location and extent of the damage[4].

The presence of ischemia, injury or infarction (necrosis) patterns in the ECG depends on the percentage of coronary obstruction, myocardial oxygen demands, length of the ischemia and potential reperfusion. When myocardium is exposed to a short period of ischemia ATP-depending pumps (Na+/K+ ATPase) and ion channels ATP dependant stop functioning appropriately, this leads to complex intracellular mechanisms that diminishes myocardium contractibility transitorily (myocardial stunning)[9].

Ischemia leads to an impediment of the action potential to start repolarization from epicardium to endocardium as usually happens, instead it starts in endocardium and spreads to epicardium. This abnormal repolarization is evidenced in the ECG as a T wave inversion (opposite to QRS complex polarity) or symmetric high amplitude T waves. (Figure 3)

By the other hand, injury is given when a moderate ischemia period affects the myocardium or when short but multiple ischemia periods occur. Until this point the myocardial damage is still reversible with adequate management or potential spontaneous revascularization via tissue plasminogen activator and endogenous fibrinolysis. If the injury is transmural or subepicardial it shall cause an ST segment elevation pattern in the ECG and if it is subendocardial to an ST segment depression pattern. (Figure 3)

Figure 3. Electrocardiography patterns of ischemia, injury and necrosis



Finally, when myocardium is submitted to a prolonged period of ischemia (more than 30min) due to important coronary obstruction myocardial cells suffer irreversible damage turning to infarcted cells which are dead and electrically unexcitable. This necrotic tissue cannot conduct action potentials causing important changes in the magnitude and direction heart vector.[10]

The ECG patterns is a deep Q wave more than 25% of R wave in leads I and II and more than 15% of R wave in leads V5 and V6 that usually appear within day/days of the onset of signs and symptoms. In contrast with ischemia and injury ECG patterns, deep Q waves due to necrosis (and posterior fibrosis) persist permanently.

At this point we return to the Non-Q-Wave Myocardial Infarction definition in which it is considered as an acute coronary syndrome characterized by the onset of signs and symptoms, detectable cardiac biomarkers but absence of deep Q waves after days of the ischemic episode.

This definition embraces the concept of infarction (Non-Q-Wave Myocardial Infarction) without ECG evidence of necrotic myocardial tissue or fibroblasts with fibrosis (infarcted/fibrotic cells which are electrically unexcitable).

This matter has been previously discussed by several authors such as Bermúdez Arias et al., whom expressed in

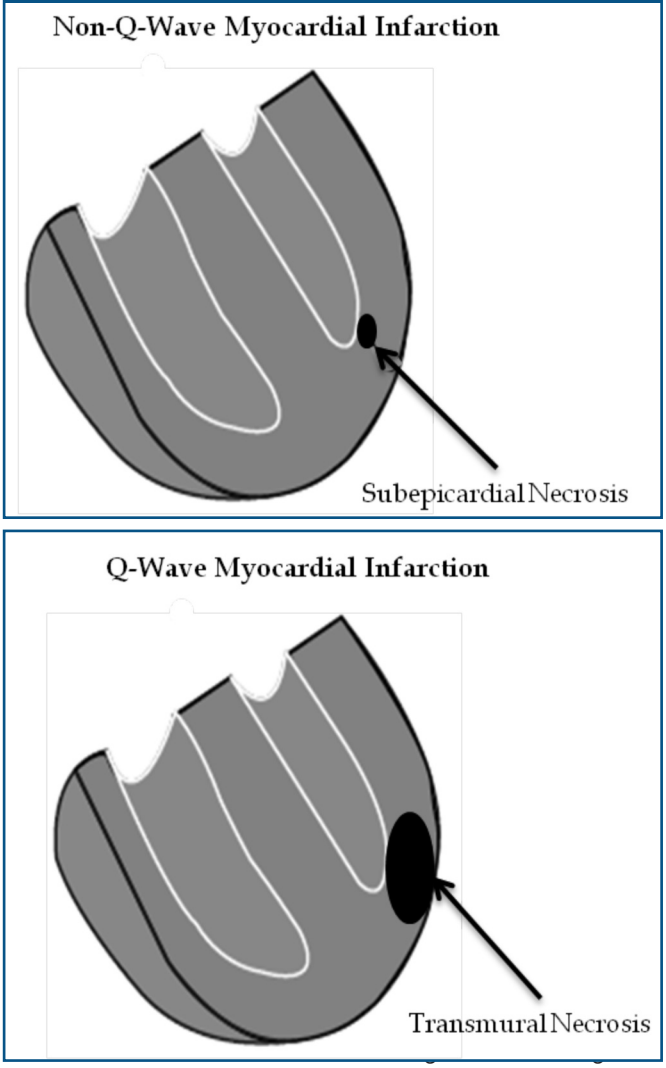
their book Cardiopatía Isquémica, "It holds our attention that concept of infarction without unexcitable zone; from a pathological and electrocardiographic point of view the denomination of infarction is only possible when there is presence of dead and unexcitable zones".

NON-Q-WAVE MYOCARDIAL INFARCTION: DEFINITION AND PATHOGENESIS

Before nowadays of fibrinolytic management and coronary care units physicians divided patients with Myocardial Infarction into two different categories those suffering a Q-wave and those suffering a non-Q-wave infarct on the basis of evolution of the pattern on the electrocardiogram over several days. The term Q-wave infarction was frequently considered to be synonymous with transmural infarction, whereas non-Q-wave infarctions were often referred to as subendocardial infarctions[7].

This line of thought is supported for the works of Wood, Wolferth & Bellet in 1938 whom defined NQwMI as a lateral and subendocardial myocardial infarction and years later for Prinzmetal et al., in 1956 whom reported that QWMI where transmural infarctions and NQwMI where subendocardial.[11] (Figure 4)

Figure 4. Non-Q-Wave Myocardial Infarction and Q-Wave Myocardial Infarction according to Prinzmetal et al.



resonance imaging indicate that the development of a Q-wave on the ECG is determined more by the size of the infarct than the depth of mural involvement. In a recent study Moon et al., studied 100 patients with myocardial infarction to whom a cardiac magnetic resonance imaging (MRI) was performed after the event.

They observed that 28% of the patients with subendocardial myocardial infarction showed deep Q waves in the ECG and inversely 29% of the patients with transmural necrosis did not show deep Q waves concluding that this distinction (QW vs. Non-QW) was useful, but it is determined by the total size of the myocardial necrosis rather than transmural extent of the underlying MI[12].

One of the proposed explanations to this ECG phenomenon is that in fact there is an important coronary obstruction that compromises myocardial viability but its natural history is modified by endogenous mechanisms such as tissue plasminogen activator, oxygen reactive species diminishment via superoxide dismutase, cessation of vasospasm through adenosine production and other molecular mechanisms happening before two hours of initiated the coronary flow obstruction.

A different possibility is that in the early 30 to 40 minutes of coronary flow obstruction an activation of collateral circulation supplies preserves the enough oxygen and other bio molecules offer to maintain myocardial viability not reaching necrosis and infarction. This possibility is more plausible in patients of ages more than 50 years due to their chances of developing efficient collateral circulation supply.

Several elements in fact indicate there was at least minimum subendocardial injury or subepicardial ischemia of new on set:

- Electrocardiographic patters of ischemia or injury in 55-60% of the patients.
- Anatomic lesion detectable through magnetic resonance imaging is certainly minor than that observed in transmural myocardial infarctions.
- Creatinphosphokinase peak is in 12 hours and not in 24 hours as seen in the transmural myocardial infarction, suggesting small necrosis and rapid clearance.
- 80% of NQwMI present subtotal coronary flow obstruction and 20% of patients experiences total blood flow obstruction (opposite proportions seen in QWMI). This suggests there might be an intense vasospasm compromising importantly coronary blood flow.
- Mortality rates are higher in patients with QWMI. After 1 year patients with NQwMI have higher mortality rates and after 2 years they are similar. (Bermúdez Arias et al., 2000)

Although there is no ECG evidence of necrosis in the Non-Q-Wave Myocardial Infarction the detection of cardiac biomarkers certainly indicates at least minimum citolysis of myocardial cells[13]. Even since 1991 some authors have been forward to assess a comprehensive interpretation

of cardiac biomarkers; Katus A.H. et al. studied the efficiency of Troponin T measurements in patients with acute myocardial infarction and other ACS.

They proposed that as a consequence of the high sensitivity of the test, elevated concentration were found in patients with NQwMI and in some patients with Unstable Angina and not necessarily meant extensive myocardial necrosis.

Also they clarify that due to the design and scope of their research it could not be determined if this high troponin T concentrations indicated presence of micro-infarctions undetectable by de ECG or just revealed reversible myocardial ischemia or injury[14].

Figure 5. Molecular mechanisms of myocardial ischemia

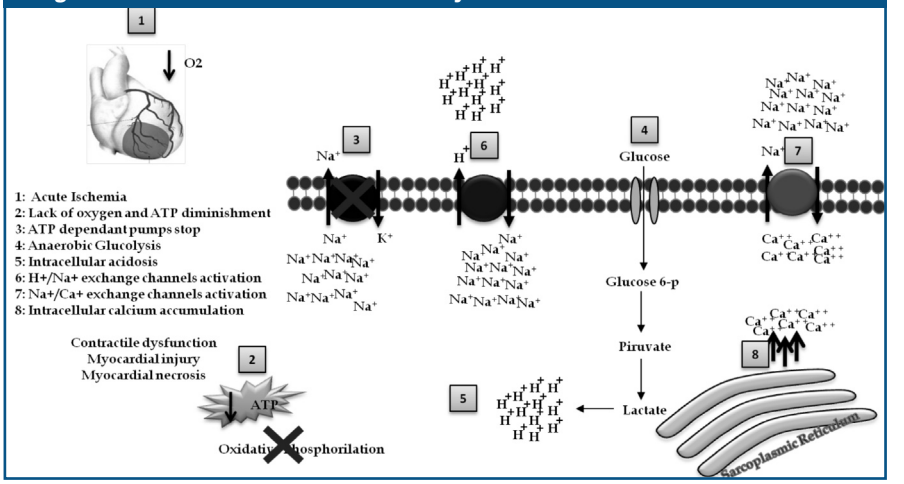


Table 2. Important differences between Q wave Myocardial Infarction and Non-Q-wave Myocardial Infarction

Variables	Q wave Myocardial Infarction	Non-Q-Wave Myocardial Infarction
Size of Infarction	Significant	Small
Ejection Fraction	Potentially diminished	Not Compromised
Reversible Ischemia	36%	60%
Re-ischemia	Less probable	More probable
Sudden dead	More likely in older than 50 years	Less likely in older than 50 years
1 year mortality	7%	20%
Recurring Angina Pectoris	20%	30%

In the VANQWISH study (Veterans Affairs Non–Q-Wave Infarction Strategies in-Hospital) carried out by Kerensky R. et al., in 2002 the evaluated the culprit lesion in 350 patients with NQwMI through coronary angiogram. A single culprit lesion was identified in only 49% of patients undergoing early angiography after NQwMI[15].

The majority of patients either had no identifiable culprit (37%) or multiple apparent culprit lesions (14%) in the angiogram. Only 36% of patients demonstrated a single incomplete occlusion of the infarct-related artery and the 84% of the patients without an identifiable culprit lesion had severe coronary disease but no complex lesion morphology.

They conclude that a single culprit lesion in uncommon (less than 50 of the patients) in NQwMI and multiple culprit lesion was seen in 14% of the patients; an angiographic culprit lesion could not be identified in more than one-third of patients[15]. These results clarify pathophysiology of NQwMI but an important group of patient remains elusive to identify the culprit lesion.

The discussion around this topic has lead many experts to consider NQwMI has a myth in the cardiology. Phibb B. et al., in their 2002 letter to the editor for the Journal of the American College of Cardiology consider NQwMI pathology has the same of QWMI: "It is difficult to imagine the NQwMI to be a distinct pathophysiologic entity when the cellular pathology is exactly the same as the QWMI"[16].

Despite the lack of a complete characterization of the culprit lesion causing NQwMI the biochemical events underlying this entity are very similar to those behind QWMI and has been well described[17]. (Figure 5)

CONCLUSION

We consider acute coronary syndromes a wide spectrum of the coronary heart disease which has been differentiated to improve clinical management according to its molecular and pathological basis. Nevertheless, NQwMI has an obscure position among these ACS's which we have tried to clarify taking into account that it is a myocardial ischemia, prolonged enough to produce cytolysis and cardiac biomarkers determination in blood stream but not extensive enough to cause abnormal deep Q waves in the ECG.

The current ambiguously of this pathological entity has led to discussion according to its pharmacological treatment and needs further research to elucidate the prime culprit lesion and then the most appropriate clinical management.

An important matter of consideration when making clinical decisions in patients with NQwMI is that these patients are a heterogeneous group in which several variables might interact. According to VANQWISH study, these patients may have single or multiple vessel coronary lesions, also important variation in ventricular functioning and cardiac biomarkers detection[18].

The non interventional approach of management includes the use of anti anginal drugs, antiplatelet drugs, lipid lowering agents, angiotensin converting enzyme inhibitors and beta-blockers.

In contrast, Halkin A. et al in 2009 studied the incidence and prognostic implications of NQwMI vs. QWMI develop-

ment following primary percutaneous coronary intervention (PCI) in 4537 MI patients with ST-segment elevation, 1230 (27%) were treated with primary PCI and discharge diagnosis of NQwMI was made in 259 (21.1%) patients. They concluded that prognosis was excellent when the diagnosis of NQwMI was done after primary PCI[19].

Whether or not to use interventional or non interventional approaches depends on the profile of the patient and available resources, nonetheless we consider of major interest the reconsideration of NQwMI definition as pathological entity and it must be an important matter in which future research and final consensus might be aimed to.

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