Dear Editor in-chief:

Thank you very much for invitation to publish this manuscript in the World Journal of Cardiology. I have considered all the comments of the reviewer and deleted, added, and changed according to the recommendations of the reviewer. Sometimes, I could not do changes and I have argued for that and I hope it will be acceptable. The changes in the manuscript as a response to the reviewer are marked by red texts. The details of my response are seen below in my response to the reviewer-

I have also submitted the figures in TIFF form separately.

I have also sent a copy of Language review, which is done by a native English researcher "Rodney De Palma" and the changes which are done in the revised main manuscript are seen as a bold blue color

With my best regards

Reviewer`s comments:

The proposal of "ANCA myocardial injury" like a new nosographic definition is very intriguing and could gather several syndromes with common pathogenesis and not grouped in the last 4thUD-MI document. Besides, some evident contradictions exist about MINOCA definition in the last published document and in the previous dedicated paper. However, some critical observations about the last UD-MI document appear to be questionable. Find enclosed document with remarks.

Author`s response:

Thank you for constructive comments by the reviewer, which surely have improved the quality of the manuscript. I have answered the questions after my best ability

Suggested corrections

Page 2

Abstract section.

Sentence: "TS and most of the 26 other causes of troponin elevation mentioned in the fourth UD-MI may erroneously be classified as *MI*".

Reply: *MI*, i.e. myocardial infarction ?!?

Comment: In 4th UD-MI published document (Eur H J 2019; 40: 237-269), TTS and other clinical conditions are grouped apart like "other causes of myocardial injury or damage (MD)" and not as myocardial infarction (MI). Generally, MD does not correspond necessarily to MI (**see fig 2 pag 244 and table 1 pag 245**)

Author`s response:

Yes, you are right in your comment but if you look at the criteria of the 4th universal definition of myocardial infarction for example the criteria of type 1 MI, which are

Detection of a rise and/or fall of cardiac troponon (cTn) values with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;

Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

If one applies these criteria on patients with takotsubo syndrome so these patients is going to fulfil these criteria. Takotsubo syndrome have also a rise and/or fall of cardiac troponon and new ischemic like ECG changes. In such a case takotsubo syndrome have the criteria of MI. The same is applied to the remainder of troponin elevations. The problem is with the criteria of MI.

I hope that I have explained the issue sufficiently

Page 3

Introduction.

Sentence: “Consequently, it is justified to raise the question, why did all the non-ischemic causes of cTn elevations should be classified as MI? In this critical review, the controversies of the UD-MI and the *confusions*, which the terms of T1MI, T2MI, T3MI, and MINOCA have caused, are explicated.”

Reply: *confusions* ?!? Maybe, between definitions in 4th UD-MI document compared to previous MINOCA ESC paper?

Comment: It is evident that 4thUD-MI document’s Authors have distinguished ischemic and non-ischemic myocardial damage. Ischemic myocardial damage has been classified as Type1, 2, 3 or MINOCA, whilst the non-ischemic myocardial damage has been grouped as “other causes of myocardial injury” (see references cited above).

On the other hand, among these several clinical conditions, the UD-MI document lacks to distinguish myocardial damage syndromes due to neuroautonomic pathogenesis (“ANCA syndromes”) from other conditions with different pathogenesis.

Author`s response:

Yes, you have right that “the 4thUD-MI document’s Authors have distinguished ischemic and non-ischemic myocardial damage. Ischemic myocardial damage has been classified as Type1, 2, 3 or MINOCA, whilst the non-ischemic myocardial damage has been grouped as “other causes of myocardial injury”

The problem again is in the criteria of different types of MI. If one apply the criteria of different types of MI on the non-ischemic causes of “myocardial damage”, so they are going to fulfil the criteria of MI and will be incorrectly classified as MI.

Yes, as you have appropriately mentioned the autonomic neurocardiogenic is not mentioned in the 4th UD-MI and I am trying to elucidate this issue

Page 4

Sentence: “the clinical diagnostic criteria of T1MI in the fourth UD-MI do not demand *invasive CAG* in all cases”

Comment: It is a right consideration, although nowadays, for a diagnostic purpose, CAG might be also replaced by non invasive coronary CT angiography (CCTA) evaluation that allows even a better definition of characteristics and morphology of the plaque than CAG.

Suggestion: the sentence could be modified in “invasive CAG (or, in alternative, non invasive CCTA) in all cases”

Author`s response:

Thank you for your suggestion. I have modified the sentence according your suggestion ahd the following is written

"the clinical diagnostic criteria of T1MI in the fourth UD-MI do not demand invasive CAG (or, in alternative, non-invasive coronary computed tomography angiography) in all cases"

Page 5
-Sentence: "…; ~~in my opinion,~~ myocardial injury is not either appropriate but probably less wrong than T2MI".

Please modify as: "It is reasonable that secondary myocardial injury is not either appropriate ….."

Author`s response: I have deleted the following sentence a "in my opinion, myocardial injury is not either appropriate but probably less wrong than T2MI."

and is replaced by

"Worth to mention, the secondary myocardial injury is not either appropriate"

Modify sentence: "T2MI has always been defined by what it is not rather than what it is" ~~. The authors have also stated~~ and that "T2MI as….
Author`s response: I have deleted "The authors have also stated" as you suggested and the following is written now
"T2MI has always been defined by what it is not rather than what it is", and that "T2MI as ……"

Modify sentence: "term MINOCA, which ~~in my opinion~~ might ~~have~~ aggravated the confusion state..
Author`s response:
I have deleted "in my opinion"

-Sentences: *"MINOCA are plaque rupture or erosion, coronary artery spasm, thrombo-embolism, spontaneous coronary artery dissection (SCAD), TS, unrecognized myocarditis, and other forms of T2MI. In principle, this implies that almost all the conditions causing troponin elevation and included in MINOCA are regarded as MI, because the MI in MINOCA is standing for myocardial infarction."*
"the authors of the ESC position paper acknowledge that the cardiac troponin is "organ specific" and not "disease specific" and that elevated cardiac troponin is not necessarily indicative of acute MI but reflects "myocardial injury". Interestingly, in 2013 when John F Beltrame [9] introduced the term MINOCA instead of MINCA (myocardial infarction with normal coronary arteries), he stated that an important first step in the assessment of patients with apparent MINOCA is to exclude the causes of non-ischemic of troponin elevations such as pulmonary embolism, acute or chronic renal failure, acute on chronic heart failure, myocarditis, "cardiomyopathies" (infiltrative, takotsubo, and peripartum), stroke, septic shock, acute respiratory distress syndrome, acute trauma (including iatrogenic), severe burns, chemotherapeutic agents and strenuous exercise. This contrasts the ESC reported causes of MINOCA [3]."

Comment: It is a right consideration, although in the last 4thUD-MI document (unlike the MINOCA ESC position paper), myocardial damage that happens in TTS, AHF, CKD or ill critical pts (all definable "ANCA syndromes") has been now described like distinct nosographic syndromes separately from MINOCA (see paragraphs 19 and 20, pages 253-254)
Author`s response:
Yes, you are right. What I have mentioned is that what Beltrame suggested is contrasting the ESC reported causes of MINOCA. I hope that this manuscript results in a serious discussion and eventually changes.

Page 6
-Sentence: "In a review of 16 CMR studies (CMR undertaken within 6 weeks) in patients with MINOCA, Pasupathy et al [12] reported CMR findings of myocardial infarction in 24%, myocarditis in 38%, TS in 16% and no significant abnormality in 21%. Consequently 76% of patients with MINOCA had no MI".

Comment: The study confirms that MINOCA is often overdiagnosed in most clinical studies because a high percentage of pts had a “non ischemical myocardial damage”, that must be not included as MINOCA (as stated in last UD-MI document) or vice versa had an ischemical damage due to a coronary obstruction (like in SCAD pts as demonstrated in VIRGO study, cited below)

Author`s response:
Thank you for this comment, which I totally agree with you. This is what I am trying to highlight

Page 6
-Sentence: “Takotsubo syndrome and SCAD are ~~2~~ two conditions among the causes of MINOCA according to the ESC position paper. Most of the patients with pure TS have no MI but have “NOCA” as in figure 1. The reverse is true in patients with SCAD where most of the patients with SCAD have MI and have obstructive coronary artery disease (CAD), ~~consequently no “NOCA”~~ as illustrated in figure 2”.

Comment: In the 4th UD-MI document, TTS has been correctly excluded from MINOCA, whilst SCAD has been reported in MINOCA when an intimal dissection and/or intramural haematoma has been overlooked. However, the ischemic damage in this last syndrome is due to flow limiting epicardial coronary obstruction and so, the SCAD inclusion in MINOCA appears to be quite questionable.

Author`s response:
You are right, and I agree with you and I have demonstrated that with a case illustrated in Figure 2

Page 7
Modify: ”Studies reporting on ~~”~~T2MI~~”~~ and MINOCA.....”
Author`s response:
I have deleted “Studies reporting on “T2MI” and MINOCA have shown that” as you suggested

Page 8
Add: ”and as mentioned above, most....”
Author`s response:
I have deleted “and as mentioned above”

Page 9:
Add: ”Emotional triggers as death of a close relative or acute grief may trigger the syndrome and hence the term ”broken heart syndrome” or ”stress cardiomiopathy”
Author`s response:
I have not used the term cardiomyopathy for takotsubo syndrome because the recent international consensus do not recommend cardiomyopathy. It is very hard to use the term cardiomyopathy for a condition which may be reversible within minutes (reported within 10 minutes indobutamine induced takotsubo syndrome),hours or days. I hope you accept my explanation

Deleted: ~~and thid happens in our daily practise as illustrated in~~ (figure 1).

Author`s response:
I have deleted “and this happens in our daily practice” as you suggested

Title: ”4B- Takotsubo syndrome in and of itself is not a MI”
Modify: ”4B- Noninfarctual evidence of Tako-tsubo syndrome”
Author`s response:
I really wanted to use the term “Noninfarctual” but I could not find this in medical dictionary and I am afraid that it will not be appropriate. In line with your thoughts, I have deleted this subtitle “Takotsubo syndrome in and of itself is not a MI” and replaced it with “Evidences for that takotsubo syndrome is not a MI”. I hope it will be acceptable

-Title:”4C- Other disease conditions reported to cause troponin elevation, what is the mechanism?”
Suggestion: “4C- Other disease conditions involved in troponin elevation”
Author`s response:

Thank you for your suggestion, I have changed according your advice. I have deleted **"Other disease conditions reported to cause troponin elevation, what is the mechanism?"** and replaced it with **"Other disease conditions involved in troponin elevation"**

Delete: "pattern ~~identical~~ similar to that of an ACS"

Author`s response:

Thank you! I have done it

Page 10

Modify: "chemical (neuromediated by norepinephrine) myocarditis"

Add: "it is usually reversible (neurogenic stunning)."

Author`s response:

I have modified and added according your recommendation.

Page 11

-Sentence: "sepsis and infectious diseases [41], stroke and subarachnoid hemorrhage [42], *chemotherapeutic agents* [26], acute critical diseases[43], strenuous exercise, pulmonary embolism, coronary spasm, acute coronary syndrome including *spontaneous coronary artery dissection* [2,32,38], chronic obstructive pulmonary disease with acute exacerbation, bradycardia and AV-block, and many others[2,32]"

Comment: Some of these conditions may have a common pathogenetic mechanism of myocardial damage like TS for including them in "ANCA syndromes". However, SCAD might be not included in ANCA syndrome, unless a SCAD and TS coexist, as sometimes hypothesized. Besides, chemioterapeutic agents and other drugs (steroids or hormons as doping use, cocaine, etc) may elicit a myocardial damage through a "direct myocardial toxicity" and not only by a neuroautonomic mechanism; so, they might not necessarily included as ANCA.

Add: "to conclude that most of the disease conditions mentioned to cause troponin elevation is directly or indirectly associated ~~in a way or another~~ to TS or TS-related syndromes discussed below."

Author`s response:

About your comment. I do not mean that they are ANCA syndrome but it is a fact that they have been reported to trigger takotsubo syndrome and for this reason I have mentioned that "most of the diseases"….. According to your recommendation, I have changed to "directly or indirectly"…..and deleted "in a way or another"

Pages 11-12

Subchapter: "4D- TS-related disease conditions

The defining feature of TS is the distinctive circumferential LVWMA, which extends beyond the coronary artery supply territory resulting in conspicuous left ventricular ballooning during systole. In addition to this fundamental feature, TS have also other characteristic features as: the repolarization electrocardiographic (ECG) changes as ST elevation or depression, peaked or inverted T waves and corrected QT prolongation[46]; modest troponin elevation with a rise and/or fall pattern; patchy late gadolinium enhancement or myocarditis like changes on CMR imaging (chemical, nor-epinephrine-induced)[33]; and the finding of hypercontracted sarcomeres and contraction band necrosis on histopathological examination[37]. However, all the above-mentioned constellations of findings are not always found in TS. Many of the clinical diseases reported to cause troponin elevations, as among others stroke, subarachnoid hemorrhage [42], sepsis [41], and chronic obstructive pulmonary diseases [2], and pheochromocytoma [40] have been reported to trigger TS as mentioned above. However, the same clinical condition may cause above-mentioned repolarization ECG changes, troponin elevations, chemical (norepinephrine) myocarditis on CMR imaging, or contraction band necrosis alone or in combination without LVWMA [42]."

Comment: all these aspects are of TS are largely repetitive because already described in the previous 4A and 4C sections.

Suggestions: Simplify or delete it.

Author`s response:

This paragraph is important to argue for the ANCA mechanism in patients without LVWMA but have others features found in TS.

I have instead simplified it and reduced the number of words from 173 to 126. So, I have deleted this
"The defining feature of TS is the distinctive circumferential LVWMA, which extends beyond the coronary artery supply territory resulting in conspicuous left ventricular ballooning during systole. In addition to this fundamental feature, TS have also other characteristic features as: the repolarization electrocardiographic (ECG) changes as ST elevation or depression, peaked or inverted T waves and corrected QT prolongation[46]; modest troponin elevation with a rise and/or fall pattern; patchy late gadolinium enhancement or myocarditis like changes on CMR imaging (chemical, nor-epinephrine-induced)[33]; and the finding of hypercontracted sarcomeres and contraction band necrosis on histopathological examination[37]. However, all the above-mentioned constellations of findings are not always found in TS. Many of the clinical diseases reported to cause troponin elevations, as among others stroke, subarachnoid hemorrhage [42], sepsis [41], and chronic obstructive pulmonary diseases [2], and pheochromocytoma [40] have been reported to trigger TS as mentioned above. However, the same clinical condition may cause above-mentioned repolarization ECG changes, troponin elevations, chemical (norepinephrine) myocarditis on CMR imaging, or contraction band necrosis alone or in combination without LVWMA [42].
And replaced it with
In addition to the distinctive circumferential LVWMA, TS have also other characteristic features as: the repolarization ECG changes[46]; modest troponin elevation with a rise and/or fall pattern; patchy late gadolinium enhancement or myocarditis like changes on CMR imaging[33]; and the contraction band necrosis on histopathological examination[37]. However, all the above-mentioned constellations of findings are not always found in TS. Many of the clinical diseases reported to cause troponin elevations, as among others stroke, subarachnoid hemorrhage [42], sepsis [41], and chronic obstructive pulmonary diseases [2], and pheochromocytoma [40] have been reported to trigger TS as mentioned above. However, the same clinical condition may cause above-mentioned repolarization ECG changes, troponin elevations, chemical (norepinephrine) myocarditis on CMR imaging, or contraction band necrosis alone or in combination without LVWMA [42]
I hope that this will be acceptable

Page 12
Modify: "~~A typical example is that what happens in~~ Tipically, among patients with acute subarachnoid hemorrhage [42], ~~where~~ 70% may ~~have~~ show left ventricular diastolic dysfunction, in 67% of them may ~~have~~ be present ECG changes including repolarization abnormalities ~~ECG changes~~, in 30% ~~may have~~ a troponin elevation [47], and only ~~=~~ near 20% ~~may have~~ LVWMA."
Author`s response:
I have changed to the following according your recommendation
Typically, among patients with acute subarachnoid hemorrhage [42], 70% may show left ventricular diastolic dysfunction. In 67% of them, ECG changes may be present including repolarization abnormalities, in 30% troponin elevation [47], and only near 20% LVWMA.

Page 13
Add: "…and other features seen in ~~Tako-tsubo syndrome~~ TS without causing…."
Delete: "These repeated TS episodes may ~~result~~ determine in permanent…"
Author`s response:
I have done both changes you recommended

Page 14
Delete: "from ellipsoid to spherical ~~in~~ shape"
Author`s response:
I have deleted according to your recommendation

Page 15

Modify title: “5- Evidences for hyperactivation of autonomic (sympathetic) nervous system ~~including local sympathetic nervous system and for that ANCA syndrome has a pivotal role~~ in ~~the pathogenesis of~~ TS and TS-related syndromes (“ANCA syndromes”)”

Author`s response:

I have changed the subtitle from:

Evidences for hyperactivation of autonomic (sympathetic) nervous system including local sympathetic nervous system and for that ANCA syndrome has a pivotal role in the pathogenesis of TS and TS-related syndromes

To

Evidences for hyperactivation of autonomic (sympathetic) nervous system in TS and TS-related syndromes

Page 17

Delete: “rapid resolution of LVWMA, ~~which~~ occurred at the completion of heart transplantation; ~~this rapid resolution may have to do with~~ the simultaneous surgical…”

Correct misprint: “cardiac symapathetic tone” in “cardiac sympathetic tone”

Author`s response:

Both sentences corrected according to your recommendation

Page 18

Correct misprint: “neutrally” in “neuro-mediated”

Modify: “~~That the~~ This circumferential pattern…”

Modify the title: “6-Mechanism of troponin elevation in ANCA syndromes (including TS)”

Delete: “from ~~stressed~~ hypercontracted cardiomiocytes by neuroadrenergic stimuli”

Author`s response:

All 4 sentences corrected according to your recommendation

Page 20

Modify: “coronary ischemic ~~troponins~~ mechanism and consequently MI (caused by….”

Author`s response:

This has been corrected according to your recommendation

Suggestion to modify initial conclusion:

“The clinical criteria for the diagnosis of ~~T1MI, T2MI, T3MI,~~ myocardial infarction according to the fourth UD-MI document ~~are full of controversies~~ show controversial aspects ~~have caused confusion~~ and reveal some contradictions about MINOCA definition, compared with previous ESC document. T2MI and MINOCA are not evidence based. Most of the cases included under MINOCA have no MI and some of those with MI have missed obstructive instead of non-obstructive coronary arteries….. “

Author`s response:

This has also been corrected according to your recommendation