Cardiac Events Theoretically Cannot Be Produced By Non-Ischemic And/Or Iso-Ischemic Myocardium: Challenging Postulations And Vitality Of The Concept Of “Ischemia-Dependent Conflictogenic Arrhythmias”

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Abstract
Ischemia plays a key role in cardiac arrhythmogenesis, particularly in elderly patients. Healthy, non-ischemic and structurally normal myocardium is universally free from dysrhythmias. Thereby intact coronary blood flow prevents potential cardiac events. Hypothetically, ischemia-related electrophysiological differences are responsible for the supraventricular and/or ventricular rhythm irregularities. The goal of this review is to determine the role of systemic and coronary circulatory peculiarities and their association with heart rhythm abnormalities. The current analytical review extends and enriches previous knowledge about the influence of these peculiarities on the genesis of ischemia-dependent conflictogenic arrhythmias. Different intensity of coronary blood flow resulting from stenotic obstacles or vasospasm potentially leads to the non-uniform perfusion of myocytes thus creating albeit subtle but vulnerable and powerful electrophysiologic substrate impending cardiac rhythm disturbances. Apparently, the behavior of both non-ischemic and iso-ischemic myocardium in respect to electric cardiac activity is very similar, at least theoretically. Some different clinical entities, e.g. arterial hypotension and/or anemia containing ischemic component, in most cases are free from arrhythmias. This postulation may be helpful in furthering arrhythmogenicity insights which have been generated previously. On the contrary, increased blood pressure often concurs with the supraventricular and/or ventricular arrhythmias; this pattern also favorably reflects our previous hypothetical assumptions associated with the mechanisms of arrhythmogenesis. Conclusively, both non-ischemic and iso-ischemic myocardium may be attributed to nonarrhythmogenic milieu. Nevertheless, the inventive analysis and more explorative data are required to support the suggested postulations.

Introduction and Principal Postulations
Under normal conditions myocardium is known to be unfavorable milieu for the manifestation of arrhythmias. In general, myocardium may be healthy or apparently healthy with different arrhythmogenic status. Perfect patency of coronary arteries along with non-ischemic myocardium itself may be treated as a natural cardioprotection from the development of cardiac events. Any arrhythmia cannot exist in the absence of corresponding susceptible substrate - ischemic, genetic, congenital, valvular, inflammatory, electrolyte imbalance or other underlying heart disease.1-6 Although atrial and ventricular rhythm disturbances have their own characteristics, variability and specificity, still there is some similarity of arrhythmogenicity preferably to those having the ischemic background. Hypoperfusion being a favorable arrhythmogenic substrate may trigger arrhythmias in both atrial and ventricular levels.7 Hence, it may be considered (at least hypothetically) that atrial and ventricular arrhythmias are probably comparable in terms of their specific ischemic etiology.

On the basis of the previous statement,1 particular emphasis has been placed on ischemia – the potential pathophysiological initiating mechanism and contributing factor believed to be responsible for the creation of the arrhythmogenic substrate. Presumably both non-ischemic and iso-ischemic myocardium warrants more or less normal electric functioning of the heart. In other words, well balanced coronary blood distribution even in reduced amounts (that happens in hypotensive and/or anemic patients) potentially undermines the manifestation of conventional arrhythmias. Regional ischemia-related electrophysiological derangements conceptually result in cardiac rhythm disturbances, though individual peculiarities may differ from patient to patient.1 In contrast, evenly distributed myocardial ischemia (or iso-ischemia) likely cannot produce arrhythmias – the phenomenon which has not been proven yet. Clinical manifestation of conventional arrhythmias (premature beats, atrial and/or ventricular tachyarrhythmias or fibrillation) may be referred to as...
ischemia-dependent conflictogenic cardiac arrhythmias. In light of ischemia–induced unfavorable cardiac events we would like to clarify several challenging conceptual statements:

- Evenly distributed myocardial ischemia (iso-ischemia or homogeneous ischemia) arising from the subnormal myocardial blood supply evokes no conflict, no arrhythmias.
- Keeping in mind the arrhythmogenicity, both non-ischemic and iso-ischemic myocardium presumably provides similar electrophysiological and behavioral peculiarities.
- Ischemia-related cardiocirculatory singularities and associated electrophysiological asymmetry as a susceptible arrhythmogenic contributor may evoke supraventricular arrhythmias within the atrial level as well as ventricular rhythm abnormalities within the ventricular level.

To our knowledge, this is the first attempt to analyze the relationship between iso-ischemia and a normal heart beat. Is the iso-ischemic condition of cardiomyocytes truly “peaceful” and non-arrhythmogenic? The potential presence of such a nexus is not well defined yet. In search of a solution and to properly elucidate this relationship along with the previously declared conceptual viewpoint, it is reasonable to analyze and collate three clinical entities, e.g. arterial hypertension, hypotension and anemia. Apparently, these entities compatibly support our viewpoint, the first of them in an antagonistic manner while the latter two – in a confirmative one. Hypertension with its well-known proarrhythmic linkage requires special interpretation. Elevated blood pressure may induce arrhythmias, such as atrial fibrillation, supraventricular and/or ventricular premature beats; decrease in blood pressure may prevent or eliminate the occurrence of cardiac arrhythmias. Contrary to what happens with hypertension, the hypotension itself demonstrates indifference with respect to inducement of arrhythmias.

Generally it is assumed that anemia is not involved in rhythm eccentricities, likely due to its equal and proportional distribution of myocardial hypoxia. Taken all together, including this observational review and by comparison of entities mentioned, we would like to finalize theoretical assumptions of arrhythmogenesis thereby convincing ourselves and the cardioarrhythmological community that the concept of ischemia-dependent conflictogenic arrhythmias is potentially valid. With that background we will seek valuable information in the available data in order to find more clinically relevant and convincing evidence.

Ischemia and its Role in Arrhythmogenesis: Basic and Clinical Evidence

There is considerable interest in mechanisms of arrhythmias arising from the ischemic heart disease. In the strictest sense “ischaemia”, derived from the Greek words, ischō (to restrain) and haima (blood), we mean insufficient blood; if we were to adhere to this definition, biological tissues which lack blood should by definition be termed “ischaemic”. Ischemia is defined as a discrepancy between the amount of oxygen supplied to the myocardium and the amount needed to ensure normal heart performance. At the moment when ischemia develops during exercise, coronary blood flow may be higher than under resting conditions, but the increase is not sufficient to meet the increased oxygen demand (demand ischemia); the situations when the entire human heart becomes ischemic (global ischemia) are relatively rare, but may be seen during severe hypotension. Importantly, in man, myocardial ischemia is most commonly regional in nature, consequently non-homogeneous excitable medium eventually may be formed.

Ischemia-induced arrhythmias have been amply demonstrated and widely recognized in laboratory and clinical practices. Arhythmogenic consequences are observed as an initial response to the coronary spasm and acute ischemia. The manifestations of coronary artery disease create distinct and time-varying changes in the myocardium that enhance the risk of arrhythmias. Numerous reports demonstrate that cardiomyocytes lacking in blood supply – oxygen, nutrients and energy – do respond to this condition by loss of local contractility and potential inducibility of atrial or ventricular arrhythmias. Some kind of arrhythmia is thought to rise from modulation of a triggering event like ischemia or electrolyte abnormalities on a preexisting anatomical and/or functional substrate.

Atrial ischemia is known to play an important role in the genesis of supraventricular tachyarrhythmias. Ischemia itself also contributes as it shortens the refractory period and decreases conduction velocity in the atria, potentially facilitating reentrant processes. Some findings suggest that atrial fibrillation may be the first manifestation of ischemia. Even the subclinical coronary artery disease is not “innocent” regarding the initiation of atrial fibrillation.

Increased myocardial oxygen demand is observed in cases of exercise or pharmacologic stress leading to the ischemia-related arrhythmias. Electrical abnormalities in diseased tissue, especially with a larger ischemic zone may initiate malignant arrhythmias. Myocardial infarction as an extreme pattern of ischemia may serve for behavioral analysis of seriously damaged myocardium. Canine and sheep models showed that acute occlusion of the right coronary artery led to atrial action potential and effective refractory period shortening. After an acute coronary occlusion, the cellular physiology of the ischemic myocardium is modified, involving changes in ion homeostasis and cell-cell coupling among other alterations. This results in reduced cellular excitability and shortened action potential, although cellular refractoriness is prolonged through lengthening of the refractory period after repolarization. Strikingly, the greater heterogeneity of extracellular K+ concentrations – and hence of secondary electrophysiological disorders – occurs at the periphery of the ischemic tissue, where gradients of both excitability and refractoriness are established.

With regional ischemia some important electrolyte imbalances and metabolic changes are confined to the poorly perfused tissue that is electrically coupled with normal myocardium at the ischemic border where injury currents flow between regions. This area, known as the border zone, has received particular attention in recent years and is increasingly thought to be the center of arrhythmic activity in the heart with regional ischemia. In early 1999, Picard et al. indicated that namely this electroanatomic location is responsible for the initiation of “border zone” arrhythmias. The membrane potential gradient between the border zone and the normal myocardium may translate into a wavebreak when the sinus wave approaches the border zone, which could lead to the formation of vortices causing cellular reexcitation; this is one of the mechanisms proposed for the genesis of arrhythmic triggers. Heterogeneities in action potential duration and altered coupling between infarct border zone tissue and surrounding myocardium create a region of conduction slowing susceptible to local conduction block necessary for reentrant excitation. The border zone of an acute myocardial
infarction undergoes the most dynamic and heterogeneous electrophysiologic transformation, thereby laying the foundations for persistent reentry phenomena; also regional ischemia significantly increases fragmentation of the activation fronts in the same zone.\textsuperscript{20,37} Similarly, arrhythmia may be evoked due to the tension arising from the electrophysiologic differences (refractory period, action potential duration, conduction velocity, excitability, vulnerability, etc. – solitary or in combination with all these factors which are most likely interrelated) taking place on the border zone, the threshold of tension may be unstable with subtle interindividual variations. These differences as key components of arrhythmogenic substrate are believed to be proximate cause which generates rhythm eccentricities. There are reports suggesting that asymmetric coronary dilatation in multi-vessel ischemia evokes coronary “steal” phenomenon which results in arrhythmic outbreaks.\textsuperscript{29,38,39} Thus, regional ischemic and electrophysiologic differences being concentrated in the confronting border zone (most conflictogenic area) likely are fundamental in cardiac arrhythmogenesis. Theoretically, cancellation of these differences might result in restoration of normal myocardial functioning.\textsuperscript{8}

Finally, the initiation of arrhythmia is likely provided by a combination of constituent parts which are delineated as follows: 1) precursor - intracoronary obstacles and/or vasospasm as a predisposing pathophysiologic mechanism and risk factor; 2) emergence of ischemic myocardium as a parent material setting the stage for the arrhythmia – an important initial phase which could be named “moment of creation” or “in statu nascendi”; 3) proximate cause – emergence of the electrophysiologic differences and corresponding tension on the border zone; 4) conflict – “firing” on the border line in a form of premature wavefront(s) which under proper conditions may result in unorganized cardiac rhythm. Let’s continue to seek more clinically relevant information.

Hypertension and Arrhythmias

Arterial hypertension is commonly associated with cardiac arrhythmias and with and without concomitant cardiovascular disease; experimental and epidemiological studies have demonstrated potential links between hypertension and atrial and ventricular arrhythmias.\textsuperscript{9,10} The relationship between hypertension, arrhythmias and cardiac mortality also has been well defined by other investigators (10). Importantly, normotension may also generate arrhythmias in subjects with left ventricular hypertrophy\textsuperscript{40} or other underlying structural heart disease. A number of studies have indicated that functional and anatomic rarefaction of microvessels occurs in hypertension.\textsuperscript{41} An impaired coronary perfusion in hypertensive patients is also important in rhythm abnormalities mainly due to the tissue perfusion restriction.\textsuperscript{42} Antihypertensive therapy is associated with a reduction in both ventricular and supraventricular ectopy.\textsuperscript{10} Patients with hypertension of several years standing have increased peripheral vascular resistance.\textsuperscript{43} The increase in this resistance is present in all vascular territories including coronary arteries.\textsuperscript{42} The lumen diameter as a ratio of wall thickness is reduced in small arteries in all forms of hypertension.\textsuperscript{42} Thus, maximum vasodilatation (minimum resistance) is reduced; which results in a reduced vasodilator reserve (most significant in the coronary circulation) and vasomotor responses are enhanced, as a given shortening will induce an exaggerated vasoconstriction.\textsuperscript{44} Also there is a reduction in microvascular density however it is still unclear whether this is related to “functional” (non-perfused vessels) or structural (obliterated vessels) changes.\textsuperscript{42} It is likely that persistently non-perfused vessels are ultimately obliterated.\textsuperscript{41}

Noteworthy, hypertensive patients have a high propensity to develop rhythm irregularities. Elevated blood pressure facing coronary narrowing along with increased coronary wall tension according to the Laplace’s law\textsuperscript{42} most likely provide synergistic effects and can alter ischemic manifestations thus evoking conflict between regions having different ischemic and electrophysiologic status. Obviously, biomechanical, morphological and physiological features of great arteries as well as of cardiac vessels may significantly influence the myocardial response.

The aforementioned literature sources demonstrate the presence of ischemic areas or foci occurring and likely activated on the basis of increased blood pressure. Hypothetically, high blood pressure in concordance with coronary heart disease leads to increase in differences of electrophysiologic tension at the ischemic border zone. Consequently, it leads to the decrease in electrophysiologic tension threshold finally resulting in ectopy.

Benign/Neutral Cardiac Response to Hypotension and/or Anemia

As stressed above, hypertension often results in arrhythmias – supraventricular and/or ventricular. In contrast, hypotension (drug related or due to arterial bleeding) eliminates ventricular ectopy both in animal and clinical studies; which is why lowering the blood pressure by simple means may be beneficial to the arrhythmia.\textsuperscript{4} There are reports indicating that in patients with orthostatic hypotension cardiac arrhythmias may take place in cases of preexisting hypertension and coronary artery disease.\textsuperscript{46} Noteworthy, cardiac arrhythmias per se, such as long runs of premature beats, supraventricular and/or ventricular tachycardia (sometimes called “arrhythmia-related hypotension”, “arrhythmias provoking hypotension”, “rate related hypotension”, “hypotensive arrhythmias”, etc.) can compromise the patient’s hemodynamic status by reducing cardiac output finally resulting in hypotension.\textsuperscript{47}48 Similarly, tachyarrhythmias may decrease diastolic filling and reduce cardiac output, leading to hypotension, and increase myocardial oxygen consumption, thus producing myocardial ischemia;\textsuperscript{48} management includes correction of existing imbalances and medical therapy directed at the arrhythmia itself. Hence, arrhythmias may precede hypotension, the latter one being secondary to arrhythmias. According to Baretti et al.\textsuperscript{13} every arrhythmia will disturb nearly perfect evolutionary design of the heart and its two successively working pump chambers. In fact, rhythm abnormalities may produce hemodynamic instability due to the compromised global cardiac mechanical efficiency. Thus, hypotension does not generate rhythm abnormalities, however arrhythmias themselves potentially are responsible for the decreased blood pressure.

Anemia reduces tissue oxygen delivery and causes a compensatory cardiovascular response.\textsuperscript{41} Tuncer et al.\textsuperscript{55} also have shown that physiologic response to anemia is a compensatory increase in cardiac output through increases in blood volume, preload, heart rate, and stroke volume, along with a decrease in afterload. Anemia is usually associated with a benign course from the standpoint of rhythm disorders. Anemia leads to global, however proportionally distributed myocardial hypoxia thus evoking no dysrhythmic eccentricities. In other words, no arrhythmia may appear in spite of whether
Anemia. Nevertheless, “choking” of the entire heart is to be treated of the human body do not benefit either from hypotension or their “neutrality” by producing no cardiac arrhythmias. Apparently, or tolerable. Mild hypotension and/or anemia may demonstrate tolerable levels - are relevant in saving of cardiac rhythm. No risk subnormal parameters – low pressure and low hemoglobin within inappropriate blood and oxygen supply to myocardium, however

In experimental dogs, after arterial bleeding compensated for volumetric parameters by fluid infusion, there were no premature beats observed – neither atrial nor ventricular – during 24 hours of Holter monitoring. Anemia usually leads to increase in heart rate, most often in sinus tachycardia. Athanasios et al. have observed patients with cardiovascular adaptation to chronic anemia without the expected increase in heart rate. In response to increased heart rate, myocardial cells dynamically adapt (shorten) their action potential duration. Some investigators have shown that chronic severe anemia in the absence of cardiac comorbidity was well tolerated by the older individuals without development of congestive heart failure, even in patients with hemoglobin as low as 5.0 g/dL; interestingly heart rate was not significantly different between anemic patients and controls. Also no significant difference was observed in heart rate variability parameters between patients with anemia with limited physical activity and healthy ambulatory population. Specific adaptive mechanisms allow healthy humans to tolerate severe degrees of normovolemic anemia, although side effects, such as arrhythmias or ST-segment changes can be observed in extreme cases. There are reports indicating that in anemic humans premature atrial contractions and/or atrial fibrillation occasionally may take place, however it is uncommon, particularly in the absence of coronary artery disease. In some patients with chronic anemia the premature atrial beats, nonspecific ST-T changes, mild conduction disturbances were recorded. Such abnormalities appeared when hemoglobin fell below 7 g/dL and vanished after its restoration to normal concentrations. It is considered that in the absence of heart disease cardiac functional abnormalities begin to appear when the hemoglobin concentration falls to below 7 g/dL. Some clinical observations demonstrate the absence of atrial extrasystole, atrial tachycardia or atrial fibrillation in patients suffering from chronic anemia, according to researchers some electrocardiographic changes arise from combined reasons – from myocardial ischemia and anemia. Anemia and arrhythmias in critically ill patients may increase annual mortality rate. Obviously, both hypotension and anemia result in ambiguous and inappropriate blood and oxygen supply to myocardium, however subnormal parameters – low pressure and low hemoglobin within tolerable levels - are relevant in saving of cardiac rhythm. No risk criteria with respect to the degree of the hypotension and anemia have been established, but some shifts or fluctuations may be neutral or tolerable. Mild hypotension and/or anemia may demonstrate their “neutrality” by producing no cardiac arrhythmias. Apparently, the whole cardiovascular system as well as organ systems and tissues of the human body do not benefit either from hypotension or anemia. Nevertheless, “choking” of the entire heart is to be treated as a more favorable clinical condition in comparison to the regional myocardial “suffocation”. Thus, adverse cardiac effects arising from the hypotension and anemia may be mitigated or neutralized by fluent coronary circulation. Undoubtedly, benign behavior of these clinical entities does have its limits. Patients suffering from critical hypotension as well as anemia and requiring resuscitation measures may be potentially proarrhythmic. Obviously, when systemic hypoxia drifts toward anoxia, clinical situation may worsen dramatically. Anemia in combination with ischemic heart disease may be considered a significant risk factor for rhythm disturbances and higher mortality rate. Thus, severe iso-ischemia leads to severe consequences, therefore benign iso-ischemia progressively may be converted into a “malignant” one, finally resulting in life-threatening arrhythmia. These issues should be taken into consideration during the evaluation of the entire cardiovascular condition but likely may not be applied to all patients.

Conclusions:

Normal coronary blood flow may be treated as a nonspecific cardiac protective factor against arrhythmias. The findings of this review in aggregate encompass more penetrant insights into the mechanisms of the arrhythmic substrate formation. Referential literature is in favor of hypotension and/or anemia as it warrants stable or relatively stable heart rhythm. It appears that these clinical entities fundamentally corroborate our conceptual viewpoint regarding the regional ischemia–dependent arrhythmogenesis. The mainstay of the current conceptual postulations is however the absence of intracoronary obstacles along with reduced coronary blood supply; such a specific and relatively robust cardiovascular condition actually is defined by global not regional cardiac ischemia. Thus, hypotension and/or anemia in their mild forms lack capability to arrange the ischemic areas within myocardium, therefore cardiomyocytes potentially cannot generate arrhythmias. Inadequate however well distributed, myocardial perfusion promotes a benign clinical course in respect to rhythm disturbances. Decreased blood pressure and/or anemia in combination with the obstructive coronary artery disease may stipulate any arrhythmic manifestation. No doubt, rhythm abnormalities are strongly influenced by regional myocardial ischemia. Hypertension and accompanying rhythm disturbances reflect the presence of regional ischemic areas or foci which, in turn, are responsible for the arrhythmic outbreaks. As an endpoint and contribution of this article might be discreet postulation that both non-ischemic and/or iso-ischemic myocardium are non-arrhythmogenic. Although the vitality of the concept of “ischemia-dependent conflictogenic arrhythmias” was substantiated by clinical entities mentioned above, this phenomenon deserves further scientific research. It may open new clinical perspectives in cardioarrhythmology.

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