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From Incidental, Mechanically-Induced Arrhythmias to Reflex-Defined Arrhythmogenicity: On The Track of The Ternary Reflex System Resemblance to The "Infancy" of New Era or Rediscovery

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Abstract

The underlying pathophysiology of supraventricular and ventricular arrhythmias remains a matter of intense investigation. Though evolving, the contemporary explanations do not encompass all aspects of arrhythmogenicity. An improved understanding of arrhythmia substrate is needed to augment therapeutic capabilities. Our observation and literature sources demonstrate relatively high incidence of transitory arrhythmias which are non-intentionally generated by the endocardial lead/catheter manipulation. These findings are interesting and potentially may crystallize the reflex-dependent proarrhythmic cardiac activity. Herein we suggest the "reflexogenic arrhythmogenicity" concept extending an overall spectrum of known hypotheses. Cardiovascular reflex action can be categorized into three-tiered levels – intra-cellular, inter-cellular and inter-organic. The first two levels of the triplicate system reside within the cardiac anatomical landmarks (in fact intramurally, intra-organically), however the third one implicates central (cerebral) activity which boomerangs back via centripetal and centrifugal connections. These levels likely compose synoptic ternary reflex set system which may be validated in future studies. To hypothesize, coordinated mutual reciprocity of reflex activity results in stabilization of heart rhythm in robust heart. Any stressful cardiac event may lead to the shift of the rhythm toward unfavorable clinical entity probably via the loss of the influence of dominant reflex. Overall, an interaction and likely intrinsic inter-tiered competition along with possible interplay between physiological and pathological reflexes may be treated as contributing factors for the inception and maintaining of arrhythmias and cardiac performance as well. These assumptions await further documentation. If such a tenet were recognized, the changes in the clinical approach to arrhythmia management might be anticipated, preferably by selective reflex suppression or activation strategy.

Introduction

Some conceptual mechanisms of arrhythmogenesis and differences between automatic and triggered rhythms remain moot.[1] According to current knowledge cardiac arrhythmias as well as atrial fibrillation (AF) most often stem from the ischemic or cardiomyopathic areas or on genetically determined basis, but overall underlying pathogenetic mechanisms are not completely understood yet. The mechanisms responsible for cardiac arrhythmias are generally divided into 2 major categories:

(a) enhanced or abnormal impulse formation and

(b) conduction disturbances.[2] Basic derivatives of existing hypothetic explanations – focal, triggered activity, micro- and macro re-entry, circus movement, spiral waves, meandering waves, rotors, multiple wavelets, delayed afterdepolarizations, double layer hypothesis, bifurcated theory, etc.[3-9] do not cover all aspects of vulnerable substrate of supraventricular and ventricular arrhythmias.

Invasive intracardiac procedures are often accompanied by rhythm eccentricities. Premature contractions are typically induced by mechanical touch - pressure or trauma - to the endocardium. Dysrhythmia being interventional in nature usually resolves when irritation discontinues. Both atrial and ventricular arrhythmias may occur and disappear under similar circumstances. These observations are interesting and may herald new conceptual insights into the arrhythmogenicity.

The musculature like any muscle cell, including myocardial ones, is implicated in motor effects in response to many inputs or stimuli - electrical, mechanical, thermal, neurohumoral, metabolic, pharmacological, toxic, ischemic - hypoxic, hyponutritional, etc.[10-16] Specific sensitive receptors are involved in activating the reflex circuit.

Knee jerk – a kick reflex is produced by sharply tapping the patellar ligament.[17] Similarly, cardiac motor effects – premature cardiac contractions – are posed by endocardial lead impingement on atrial or ventricular wall.

The primary goal of the article is to sketch out a universal theory

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which potentially might explain, at least in part, the pathophysiology of arrhythmologic substrate. To stress the reflex-dependent arrhythmogenicity and to facilitate its descriptive explication we start with the leveling of several semantic definitions which are close to identical:

(1) cardiac/cardiovascular autonomic control,

(2) cardiac/cardiovascular reflex regulation, and

(3) automaticity. In normal cardiologic state these definitions can be interchangeable and might be interpreted as a natural reflexogenic or reflex-dependent cardiac activity. Hypothetically, cellular automaticity, cardiovascular reflex activity and autonomic nervous system functions are uniquely condensed for precise tuning of heart rhythm. Any pathological cardiac event (ischemic, cardiomyopathic, structural, inflammatory, etc.) likely interferes with functionally well-organized harmony, thus paving the way for rhythm disturbances.

New insights into arrhythmogenic milieu presumably could contribute to better comprehension of complex nature of arrhythmogenesis. This analysis is intended to contribute to our evolving understanding of the arrhythmia mechanism and enrichment of existing hypotheses. Prior to accepting the proposed hypothetic approach an assessment by independent studies is needed to validate the postulations that are construed on a deductive basis.

Background and General Reflections

Any accidental insertion of the pacing lead into the pulmonary artery or ventricular outflow tract often results in firing of chaotic premature ventricular beats leading occasionally to critical destabilization of heart rhythm. Supraventricular extrasystoles or premature atrial contractions are incited less often by an atrial lead compared to a ventricular one. Risky manipulation of the lead resulting in provocative cardiac response is thought to be relatively benign. Immediate release of the lead usually solves the problem. Lingering maneuvering however, may result in severe problems. The character of evoked dysrhythmia may vary considerably from patient to patient. Non-intentional induction of cardiac activation prematurity in general is highly reproducible and may serve as endocardial or intramural activation pattern during mechanically induced stress. Most likely the arrhythmia is elicited by the whip or abutting the cardiac wall by the lead. This statement comes from personal experience and perception that this type of mechanical triggering of the areas mentioned may be associated with arrhythmia manifestation on purely reflexogenic basis.

We are not alone when it comes to empirical observations of premature contractions evoked by lead maneuvers. Mechanically-induced cardiac arrhythmias and mechanoelectrical feedback are well described.[18-20] Ventricular arrhythmias during catheterization of right heart chambers or pulmonary artery are extremely common.[21-23] Catheter-induced atrial or ventricular arrhythmias are potential but poorly understood complications.[22,24] According to Jie et al.[20] regional ischemia is responsible for the genesis of mechanically-induced ventricular ectopy and the mechanisms by which it degrades into spontaneous arrhythmia. Perceptible mechanistic pressure or even a gentle touch by lead on endocardium or intima of pulmonary artery actually evokes myocardial deformation and local micro-ischemic subtlety. It is still unclear which stimulus plays the dominant role - whether mechanical or ischemic impact, or both. Hypothetically, immediate cardiac response to the mechanical impact refers to as potential affliction of sensitive mechanoreceptors along with reflex or reflexes, rather than ischemic ingredients. Despite the ischemic factor providing a strong incentive for cardiac events, not every ischemic attack produces extrasystole or more serious rhythm disturbances. Though uncommon, there are well-known silent ischemia manifestations with angina-free course and arrhythmia-free one as well.[25,26]

According to our observations the intracardial manipulation by lead does not evokes dysrhythmia in every patient. It depends perhaps on allocation and high distribution variability of sensitive receptors. Absence of anatomic, ischemic, electrolytic and genetic substrate suggests the presence of other arrhythmia causes, one of which might be reflexogenic. Dube and colleagues[27] have observed premature ventricular contractions (ventricular bigeminy) immediately after application of the Valsalva maneuver. Again, it suggests that arrhythmias, at least some of them, may originate on reflexogenic basis.

Key Characteristics of Reflexes

It is well established that any muscular activity, be it skeletal, cardiac or smooth one is actually influenced by reflex control.[10, 11, 17, 28] In general, it is improbable that the human heart as a key muscular organ might be out of reflex regulation: it may be considered as an obvious, time-tested axiomatic truth. There is a long list of reflexes with 336 positions attributable to humans.[29] First of all let's look at skeletal muscles and their behavior under the influence/participation of reflexes.

The classical knee jerk (knee reflex) represents the group of so called physiological reflexes.[17] There are also pathological reflexes, e.g. Babinski's sign[17, 30] reflecting the presence of corresponding illness. Aberrant reflexes indicate spinal cord injury.[31] Clinicians often observe symptoms and signs entitled hyperreflexia, hyporeflexia and areflexia.[32] Hypothetically, assumptions associated with reflexes relevant to skeletal muscles may be extrapolated to the cardiovascular system and specifically to the myocardium.

The cardiovascular system nevertheless is "equipped" with the physiological reflexes, e.g. Bainbridge, Bezold-Jarisch, etc.[10, 17, 33] Clinicians are familiar with "reverse" Bainbridge reflex.[33] The mechanoreceptors that elicit this reflex are located at the junction of the right atrium and caval veins or at the junctions of the pulmonary veins and the left atrium;[34] this reflex is controversial, however, because its existence cannot always be demonstrated. The Bezold reflex effects are implemented through complex transformers, transducers and encoders being incorporated into the central feedback mechanism and affecting sensory input at receptor level.[10, 35]

Pathological and aberrant reflexes which might be attributed to the cardiovascular system are still unknown, just "pathological reflex effects" are mentioned.[36] To cover all aspects of cardiovascular regulatory system the pathological reflexes as such hopefully will be discovered. Cardiac contractile tissues like skeletal muscles may potentially demonstrate the presence of pathological reflexes especially in critical cardiac situations or at least on a virtual basis. Thus, coexistence of several kinds of reflexes, including hyper-, hypo- and areflexia, may lead to functional cardiac confusion, hence, to unpredictable consequences.

Fundamental Reflex Physiology

Reflex is an automatic, boomerang back response to a stimulus or changes within or outside the human body. Reflex is typically fast and involuntary, because most reflexes do not require much brain activity.

The reflex circuit or reflex arc compose a feedback loop and has two general components: one is for sensory purpose, and the other is for the motor/response one. In general, reflexes and autonomic nervous system are helpful in any cardiorespiratory and somatic adaptation which is stated in textbook manuals analyzing reflex regulation of various organ systems including muscular or cardiovascular one.[17,37,38]

The cardiovascular system is subject to precise regulation so that an appropriate supply of oxygenated blood can be reliably provided to different body tissues under a wide range of circumstances.[28] The afferent information from changes in arterial pressure and blood gas levels reflexively modulates the activity of the relevant visceral motor pathways and, ultimately, of target smooth and cardiac muscles and other more specialized structures.[28] Cardiac autonomic nervous system consists of two branches – the sympathetic and parasympathetic systems – that work primarily through actions on cardiac pacemaker tissue in a delicately tuned, yet opposing fashion in the heart.[16, 37] Hence, the concept of accentuated antagonism has emerged to define the functional relationship between these systems.[39, 40] Hasan[16] has stressed that the crosstalk between both limbs of the autonomic nervous system is critical for maintenance of normal cardiac rhythm and function. The author has concluded that: examination of the mechanisms involved in the development of these intimate connections will potentially allow therapeutic approaches to be harnessed for reversing breakdown in these communications in diseased states. The work by Vaseghi and Shivkumar.[37] showed that both sympathetic and parasympathetic nervous systems are intricately involved in the modulation of cardiac excitability and arrhythmias; neural remodeling creates the electrophysiological substrate necessary to initiate and maintain arrhythmias. It is well-known that imbalance in the autonomic regulation of heart rate is characterized by enhancements and decrements in sympathetic and parasympathetic activity, respectively.[41, 42] In other words, sympathetic and parasympathetic impulses drive the heart rate pursuant to sinus node functional demand and, as mentioned above, do participate in modulation of myocardial excitability and arrhythmias.

Circulatory reflexes are integrated at various levels of the central nervous system or "central command";[38, 42] important role play mechanoreceptors located in the atria and ventricles being sensitive to mechanical stretch. Thus, it may be postulated that whenever muscles are involved we deal with reflexes irrespective of whether the muscles represent voluntary or involuntary pattern. Undoubtedly, the reflex participation in the regulation of any muscle activity including cardiac one is very important, even if still underestimated.

More discussions is needed to elucidate proper cardiovascular regulation via autonomic nervous system. According to contemporary knowledge, intracardiac and/or intravscular signals are transferred centripetally through neurohumoral, baro- and mechanoreceptors. In skeletal muscle fibers the refractory period is about 1 ms to 2 ms in duration; the total refractoriness – absolute+relative – of about 2 ms to 100 ms, whereas the cardiac muscle refractory period reaches 150 ms to 300 ms.[43] Interposition of the refractoriness (also anisotropy being common in damaged myocardium) in the complex chain - myocardium, afferent and efferent limbs – makes the reflex action less pliable and less adaptive. Nevertheless, the refractoriness represents an indispensable component to secure the stability of heart rhythm, otherwise malignant tachyarrhythmias may develop. Typical interference of refractory window actually allows the myocardium to regain its contractility power. Reportedly, the changes in duration of the refractory period may affect cardiac performance significantly.[6, 14, 44] Micro- and macro- structural heterogeneity, anisotropy as well as the shift of the refractoriness are observed in diseased myocardium.[6, 45, 46] That is why, due to anisotropic architecture of most myocardial regions,[47] the "reflexogenic arrhythmogenicity" remains to be explored more precisely.

Novel Debatable Insights

While arrhythmias vary widely in their clinical presentations, they possess shared electrophysiologic properties at the cellular level.[6] Talking about reflex activity in general, first of all we consider automatic reflex mediated mechanic cardiac response to any selective stimulus. If we were to accept the theory by which the reflexes contribute to cardiac arrhythmogenicity, consequently the synoptic concept of three-tiered/ternary reflex system might be suggested. This concept defines different levels of autonomic components - reflexes with different length of their limbs participating in healthy and diseased cardiac/cardiovascular regulation. According to the reflex arc's span the limbs may be categorized as ultra-short, medium and long. Thus, the first level is represented by intracellular reflexes ("eponymously" known as cellular automaticity, triggered, focal, ectopic activity). Hypothetically the receptors along with the afferent and efferent reflex limbs reside inside the pacemaker cell(s). The second level might be referred to as inter-cellular (intraorganic, intracardiac, intramural) reflexes demonstrating their activity via cell-to-cell communication (per intercalated discs, genuine conduction pathways, also accessory pathways). Therapy may be implemented by the disruption of conduction system elements or anomalous accessory pathways. The presence of pathological inter-cellular reflexes may partially be explained by the appearance of arrhythmias' in denervated transplanted hearts. Finally, the 3rd tier might be characterized as inter-organic reflexes integrated into hegemonic centers. The latter one has close hierarchic interrelationship between the heart and central (cerebral) command centers[42] via centripetal and centrifugal connections. It can be assumed that triple protection entity (as the life protective unconditional reflex activity) may serve for survival reasons; presumably it is the result of natural human ontogenetic evolution.

Collation of Reflexes

Trilateral components – automaticity, autonomic regulatory function and reflex action/reaction operating "in corpore" potentially create a unique physiological and clinical entity.

The fundamental function defined as automaticity of pacemaker and non-pacemaker cells[6, 48] seems to be the most important feature of cardiac motor activity. Automaticity is the property of cardiac cells to generate spontaneous action potentials;[2] abnormal automaticity includes both reduced and enhanced automaticity. It appears that cardiac automaticity at the organ level is a very complex phenomenon and that, beside cellular mechanisms, integrative factors are involved in cardiac pacemaking.[49] According to Podrid and colleagues[50] the underlying ischemic heart disease evokes enhanced and/or triggered automaticity.[50] Automatism and reflexes are potentially interrelated and functionally intermingled. In other words, the functional activity of every involved tiered reflex chain(s) may be realized via automaticity. The disbalance of reflex-dependent capabilities potentially leads to proarrhythmic occurrences. Putative mechanism of overall reflex activity covers their multiple effects including crosstalk, unconditional joint action, competition or collision. Unconditional response to any

suprathreshold stimuli (incorporating "proper respect" to cardiac refractoriness) creates a specific cardioarrhythmologic scenario – normalization or degradation of heart rhythm.

The cardiovascular system is influenced by both intrinsic cardiac factors and extrinsic noncardiac ones. Chief among these is the autonomic nervous system, which mediates signals from physiological "sensors" in the heart and great vessels, such as baroreceptors, stress receptors, and various chemoreceptors.[51] Shusterman and colleagues in early 1998[52] have demonstrated that atrial arrhythmias, such as atrial fibrillation, have a long-established relationship with the autonomic nervous system, including associations with both sympathetic and parasympathetic signaling. This association has been extended to primary ventricular arrhythmias.[51]

Physiological reflexes largely orchestrate and control the heart rhythm normalcy. Arrhythmias conceivably are initiated by the substrate vitalizing pathological reflexes. The triggers residing in cardiomyopathic/ischemic areas are responsible for arrhythmic outbreaks most likely via corresponding micro- or macro-reflex arcs. It may happen by solitary pacemaker cell micro-reflex activity or by interference of upper level reflexes finally resulting in "mixed, bifunctional or trifunctional confusion". The arrhythmogenic scenario presumably may be "enriched" by hyper-, hypo-, or areflexia making corresponding myocites more or less excitable. Complex interactions between physiological and pathological reflexes actually may lead to unpredictable consequences including exhibition of pro-arrhythmic chaos. Any stressful cardiac event can alter myocardial excitability and eventually predispose to arrhythmia. Regarding the degree of myocardial damage and the amount of deactivated/destroyed sensitive receptors the cardiac responses may be mild, exaggerated or stormy, also acute or chronic. Such a viewpoint actually necessitates a new term – reflex activation threshold or reflex sensitivity parameter. The "game" of reflex capture thresholds which belongs to different dimensions, i.e. to physiological and pathological reflexes, in fact essentially creates a new milieu and new effects. Mutual/multilateral interactions and potential competition between these reflexes as well as the inter-tiered rivalry may generate both advantages and disadvantages - life saving or life-threatening outcomes. It means that we enter a virtual battlefield – "occult phenomenon" which is not explored yet and where "decision makers of arrhythmogenicity" do reside.

As mentioned above, we face well-organized and disorganized composition regarding the presence or absence of myocardial pathology. If so, the advanced myocardial pathology may exacerbate rhythm disturbances and vice versa – cardiac recovery may lead to arrhythmia regression. Furthermore, affliction of the refractoriness in general results in unpredictable functional collision of reflexes. Their integrated action does orchestrates fluently prior to occurrence of the cardiac event, however, it may result in an impairment or complete disintegration of cooperative activities with the development of an unexpected and unique electrophysiological scenario. In other words, inter-reflex turmoil after stressful cardiac crisis may emerge. Thus, reflex co-activities being harmonic in healthy myocardium and disharmonic in diseased one, presumably influence cardiac motor behavior.

Last but not least severe comorbidity in the elderly patient group may contribute secondary to arrhythmic whimsy, again via cardiovascular reflexes.

Conclusions

Cardiac premature contractions may be reproducibly incited by lead/catheter mechanical irritation of the right heart chambers. These findings are interesting and potentially crystallize the reflex-dependent proarrhythmic cardiac activity. The suggested concept of "reflexogenic arrhythmogenicity" incorporates the synoptic three-tiered or ternary cardiovascular reflex system. Cardiac motor effects like the prompt response of skeletal muscles may be reflex-determined, at least hypothetically. Complex interactions between reflex activities may provide the normal heart rhythm in healthy cardiac state, though abnormal one in ischemic or in structural heart disease. Changes in the clinical approach to arrhythmia management in light of reflex control might be anticipated preferably in terms of selective reflex suppression or activation strategy. Thorough investigation, however, is needed to assess the true value and controversies of hypothetical postulations.

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