JACC Vol. 24, No. 1
July 1994:244–6

Editorial Comment

Puppies' Programmed Sudden Death: Who Is the Serial Killer?*

PHILIPPE COUMEL, MD, FESC,
HERVÉ LE MAREC, MD†

Paris and Nantes, France

The Moise et al. (1) model in this issue of the Journal is a kind of an earliest case, if one considers that in animals the field of spontaneous lethal cardiac arrhythmias is desertic. Only T. N. James (2) described lineages of dalmatians prone to sudden death, but his observations were done at a time when one could not easily document trivial or exceptional tachyarrhythmias. Still, to our knowledge, he was actually the first to publish a record of spontaneous ventricular fibrillation in a dog. The aim of the present editorial is to comment on the perspectives offered by the Moise et al. natural dog model in terms of clinical correlates of a genetically transmitted electrophysiologic disease, its relation to the autonomic nervous system and the concomitant development of the substrate and the autonomic nervous system.

Genetically transmitted tachyarrhythmia with no structural heart disease. What comes to mind first is that this dog model might resemble the long QT syndrome or some of its variants, as it was, for instance, hypothetized in the dogs in the James study. A glance at the tracings, however, does not ring the bell for the long QT syndrome. Not only does the ventricular repolarization not look abnormal in duration and configuration, but the tachyarrhythmias do not resemble those seen in torsade de pointes. However, despite the importance of these factors, the complete absence of a relation between the Moise et al. model and the long QT syndrome cannot be entirely ruled out because of the complex nature of the latter entity, which has many imprecise aspects and probably many variants.

The repolarization looks normal, but who knows what is normal in the dog when we still have as no precise standards in humans to measure the QT interval, to adequately correct it for rate (the only consensus is to criticize the Bazett formula, although everyone uses it extensively) or to evaluate its dynamics in relation to the modulation of the autonomic nervous system. Many clinical and electrophysiologic aspects of the long QT syndrome are presently the object of active research, not only because this purely electrical disease has always fascinated the rhythmologists, but because of the impetus recently given by genetic findings (3). Many accepted notions are currently being reevaluated, and there is strong evidence (but not really surprising) that the marker that names the syndrome is probably not its most relevant characteristic. Rather than duration, the configuration and overall the dynamics of the ventricular repolarization are possibly more indicative of the potential severity, but there is still a long way to go to precisely define what the right standards are.

In the congenital or acquired forms of long QT syndrome there are no data to date to prove or disprove a cause-effect relation between repolarization abnormalities and tachyarrhythmia, namely, torsade de pointes. A variant form of torsade de pointes has just been identified (4) that indeed displays the typical electrocardiographic (ECG) characteristics and clinical absence of structural heart disease with a frequent familial history, but there is a definite absence of any T wave or QT duration abnormality. Conversely, some idiopathic catecholergic ventricular tachyarrhythmias, which may include a borderline QT interval and may cause syncope and sudden death in children of certain families, also form a variant of the long QT syndrome, but the polymorphic (often bidirectional) ventricular tachycardias do not resemble torsade de pointes even when they are confined to ventricular fibrillation (5). Other forms exist, like the syndrome recently described by Brugada and Brugada (6). Active cooperation is needed to identify the various entities because they are so rare that it is very difficult for a single team to collect enough experience on its own.

Considering the increasing number of various syndromes, it would be imprudent to conclude from the ECG pattern that the impressive tracings obtained in the dogs do or do not belong to this or that entity. The coupling interval of the first beat is neither definitely long, as in conventional torsade de pointes, nor unusually short, as in the variant form (3). The classical R on T pattern is not contributive because of its imprecision, which refers neither to T wave configuration nor to the coupling interval. The tachyarrhythmia is slightly irregular, not strictly monomorphic, but includes neither the typically twisting pattern of torsade de pointes nor the beat-to-beat changes of severe polymorphic tachyarrhythmias that occur in diseased hearts. Some caution is necessary in dogs when seeking the same criteria that we are accustomed to in humans: Different electrophysiologic conditions may explain different ECG configurations. However, the experimental models of acquired torsade de pointes offer evidence that this arrhythmia can indeed be observed in a typical form in dogs.

Arrhythmia mechanisms common to dogs and humans. That canine tachyarrhythmia does not resemble a human correlate by no means eliminates the possibility of an underlying mechanism that would be common to both species. The potential role of early afterdepolarizations in syndromes

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Hôpital Lariboisière, Paris and †Centre Hospitalier Universitaire Laënnec, Nantes, France.

Address for correspondence: Dr. Philippe Coumel, Hôpital Lariboisière, 2, rue Ambroise-Paré, 75015 Paris, France.

0735-1097/94/$7.00

including torsade de pointes (7) is more and more widely suspected. The lack of torsade de pointes pattern in the Moise et al. model is not incompatible with this phenomenon for the simple (and too often neglected) reason that there is no equivalence between this cellular mechanism and the ECG configuration of torsade de pointes. The afterdepolarization phenomenon, if any, starts from one cell, or a group of cells, and may well be followed by a triggered activity in that cell, or group of cells. Subsequently, the activation spreads to the adjacent myocardium and the whole heart in particular conditions that produce the distinctive pattern of torsade de pointes, an ECG entity that is not necessarily related to its electrophysiologic origin. One can imagine that common disorders may condition both a cellular phenomenon and an impaired intraventricular conduction so that they do not coexist simply by chance. The ECG pattern and the electrophysiologic mechanism may be linked but are indeed different entities.

What can we learn from the data reported in the Moise et al. study? Although of good quality, the investigations performed were clinically inspired, with inherent limitations. Verifying that the arrhythmias were not inducible by programmed stimulation had to be done but constitutes negative information that applies to most human severe tachyarrhythmias of purely electrical arrhythmogenic diseases. A pause-induced tachyarrhythmia is a common finding that may fit various mechanisms, including reentry as well as early afterdepolarizations.

The analysis of Holter recordings was conventional and purely quantitative. It should be refined to obtain pertinent information on the role of the autonomic nervous system. Studying the environment of heart rate is essential to understanding which conditions of the vagosympathetic balance are operating before arrhythmia onset and therefore tend to favor it. For instance, an increased heart rate in the preceding minutes or a variation of the pattern of the heart rate variability suggesting a loss of vagal tone is information that should be sought. In humans we now know that the autonomic nervous system modulates the whole spectrum of ventricular arrhythmias, ranging from benign premature beats to sudden death (8). Information obtained with regard to the autonomic nervous system in the sinoatrial node may indeed differ at the ventricular level, but this is not a sufficient reason not to look, although it may be technically difficult.

In the future, repolarization itself will have to be studied, an even more difficult challenge. We are now just at the beginning of this era. It took some time for clinicians to become aware of the importance of the role of autonomic nervous system in tachyarrhythmias and sudden death. In dogs the situation is the same, and some experimental models have proved particularly relevant (9) in clinical arrhythmias. Almost everything, however, has still to be learned about normal autonomic nervous system behavior in dogs and its development and potential abnormalities.

Perspectives offered by the present animal model. The perspectives offered by the present model of spontaneous arrhythmias are considerable. If some limitations of the present study with regard to aspects of the electrophysiologic investigations were mentioned, it was to emphasize that it will be possible to go much further, not only by mimicking the clinical situation but by using approaches that are not yet available to the clinician.

Obviously the clinical characteristics of the dog model will have to be more thoroughly explored, particularly arrhythmia behavior and the respective roles of the autonomic nervous system and cellular maturation in determining tachyarrythmias and sudden death and their timing with respect to the growth of the animals. If confirmed, the existence of a critical period for the occurrence of these accidents is crucial to understand. It is reasonable to conceive that by the third or the fourth month of life an electrogenic abnormality (an arrhythmogenic substrate) might be modulated by autonomic nervous system maturation. A few data support the hypothesis. Sympathetic innervation seems to be terminated 2 months after birth (10), and the alpha- and beta-receptors, with their coupling systems, also undergo a maturation process in the first period of life (11,12). Data concerning the vagal limb are more limited, but it seems that the muscarinic receptors also undergo a maturation process. Information concerning ionic currents and the maturation of ionic channels is also limited, but the first months of life appear to be critical for the differentiation of these channels. For instance, in the epicardial cells the outward transient current I_{to} seems to appear during the second month, precisely the period during which sympathetic innervation takes place (13). We have for the moment no information about the development of the M cells, which could play an important role (14). If the hypothesis of the joint effect of a developing arrhythmogenic substrate and its modulation by the developing innervation were confirmed, this animal model could offer a unique opportunity to investigate at the cellular level, which is not feasible in humans.

Identification and localization of the operating gene or genes in dogs is not especially rewarding for the clinician, except insofar as it implies identification of the causal ionic channel because this may have consequences common to all species. In this domain, one distinguishes the appearance of "reverse" medicine: a feedback phenomenon by which the clinician in charge of identifying the phenotype is invited by the genetician to redefine much more matters precisely. What now applies to the definition of the long QT syndrome certainly applies to the present case: In the Moise et al. model the degree of arrhythmia was used to distinguish diseased from nondiseased dogs, a criterion that is probably as approximative as, and no more relevant than, the score recently proposed for identifying patients with long QT syndrome (15). We are forced to deal with imperfect criteria: The essential point is to be aware of these imperfections because, fundamentally, an imperfect classification is better than no classification at all.

JACC Vol. 24, No. 1
July 1994:244–6

References

1. Moise NS, Meyers-Wallen V, Flahive WJ, et al. Inherited ventricular arrhythmias and sudden death in German shepherd dogs. J Am Coll Cardiol 1994;24:233–43.
2. James TN. Congenital deafness and cardiac arrhythmias. Am J Cardiol 1967;19:627–43.
3. Keating M, Atkinson D, Dunn C, Timothy K, Vincent GM, Leppert M. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey *ras*-1 gene. Science 1991;252:704–6.
4. Leenhardt A, Glaser E, Burguera M, Nürnberg M, Maison-Blanche P, Coumel P. Short-coupled variant of torsades de pointes; a new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias? Circulation 1994;89:206–15.
5. Coumel P, Fidelle J, Lucet V, Attuel P, Bouvrain Y. Catecholamine-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. Br Heart J 1978;40 Suppl:28–37.
6. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391–96.
7. El Sherif N, Craelius W, Boutjdir M, Gough WB. Early afterdepolarizations and arrhythmogenesis. J Cardiovasc Electrophysiol 1990;1:145–60.
8. Coumel P. Cardiac arrhythmias and the autonomic nervous system. J Cardiovasc Electrophysiol 1993;4:338–55.
9. Schwartz PJ, Vanoli E, Stramba-Badiale M, DeFerrari GM, Billman GE, Foreman RD. Autonomic mechanism of sudden death. New insights from analysis of baroreflexes in conscious dogs with and without myocardial infarction. Circulation 1988;78:969–79.
10. Ursell PC, Ren CH, Danilo P. Anatomic distribution of autonomic neural tissue in the developing dog heart: I. Sympathetic innervation. Anat Rec 1990;226:71–80.
11. Del Bazo U, Rosen MR, Malfatto G, Kaplan LM, Steinberg SF. Specific a_1-adrenergic receptor subtypes modulate catecholamine-induced increases and decreases in ventricular automaticity. Circ Res 1990;67:1535–51.
12. Artman M. Developmental changes in myocardial contractile responses to inotropic agents. Cardiovasc Res 1992;26:3–13.
13. Jeck CD, Boyden PA. Age-related appearance of outward currents may contribute to developmental differences in ventricular repolarization. Circ Res 1992;71:1390–403.
14. Antzelevitch C, Sicouri S. Clinical relevance of cardiac arrhythmias generated by after-depolarizations. Role of M cells in the generation of U waves, triggered activity and torsade de pointe. J Am Coll Cardiol 1994;23:259–77.
15. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. Circulation 1993;88:782–4.