IMMUNOLOGY, SCIENCE AND PUBLIC HEALTH: THE LOST LINK

To the Editor:

Immunology was born as the study of the organism's defense with the development of vaccination by the English physician Edward Jenner in 1796. It inaugurated a whole new way of looking at medical and biological phenomena, and culminated at the end of the 19th century with Pasteur's microbiological revolution. It introduced to the scientific-medical world the idea that specific infectious agents are the causes of specific diseases, and later, with Paul Ehrlich's concept of 'magic bullets', promised that certain substances would be capable of inhibiting those specific disease agents. This led to the hugely beneficial technological development of immunobiological substances and techniques, like vaccines, antibiotics, serotherapy, immunological diagnostics, monoclonal antibodies, and, in more recent years, synthetic therapeutic molecules [1]. However, applying these scientific advances to the field of public health remains a challenge.

Our new immunological therapeutic and diagnostic tools are complex, expensive, and inaccessible to many patients, who in the case of Rio de Janeiro still suffer from extreme poverty, unemployment, unclean water (30% of Rio's population lack basic sanitation, as does most of the world's population), extreme violence, and increased prevalence of infectious and chronic degenerative diseases. All these are recognized as the social determinants of health [2]. This situation reflects a profound scientific dilemma and calls for a change in perspective. We work as if the immune system was separated from the organism as a whole, and the organism separated from its family, community and society. This limited, non-contextual view represents the conventional view of immunity. It asserts that the function of the immune system is to defend the organism against invading infectious agents, and when the defense mechanisms are turned against the organism itself, autoimmune and allergic diseases occur. It fails to see other major functions of the immune system and a system integrating developmental and environmental information. However, within the field of immunology, many scientists, including Nobel Prize winner Niels Jerne, have shown that the immune system actually performs these other functions, integrating the organism's physiology [3] through a network of antibodies that bind antibodies, that bind antibodies [4]. The immune system plays a major role in tissue regeneration, cellular differentiation, blood flux, diet assimilation in the gut, and symbiotic interactions with the native microbiome. These studies show that the immune system is deeply affected by the overall physiological and psychological state of the organism and its microbiome, and this in turn is intimately connected to the mode of living, family and community life. These relations are mediated through epigenetic mechanisms that can have long-term, even trans-generational effects.

We now know that immunological defects are related to oligoclonal expansions of lymphocytes that appear in infectious and in allergic and autoimmune diseases. Oligoclonal expansions of lymphocytes have been shown to be consistently associated with epigenetic mechanisms, which in turn are affected by the environmental-social context in which organisms live [5]. These links enable the necessary dialogue between science and public medicine.

Through the encounter between immunology, cellular and molecular biology on the one hand and socioeconomic determinants of health through community and family medicine on the other, we can restore the lost link between immunology and society. I argue that a radical extension and reformulation in immunology's basic tenets is necessary. We need this change in perspective to increase the efficiency of medical and immunological strategies in the population through new public health strategies that improve the quality of medical practices and make good use of public resources.

Vitor Pordeus MD
Center for Culture, Science and Health - Public Health Office of Rio de Janeiro City; Madness Hotel and Spa - Popular University for Art and Science - Nise da Silveira Institute for Mental Health, Rio de Janeiro, Brazil and Federico Foundation, Zurich, Switzerland

References

1. Silverstein AM. A History of Immunology. San Diego: Academic Press, 1989.
2. Marmot M. Economic and social determinants of disease. *Bull WHO* 2001; 79: 988-96.
3. Vaz NM, Ramos GC, Pordeus V, Carvalho CR. The conservative physiology of the immune system. A non-metaphoric approach to immunological activity. *Clin Dev Immunol* 2006; 13 (2-4): 133-42
4. Shoenfeld Y. The idiotypic network in autoimmunity: antibodies that bind antibodies that bind antibodies. *Nature Med* 2004; 10 (1): 17-18.
5. Pordeus V, Ramos GC, Carvalho CR, Castro Jr AB, Cunha AP, Vaz NM. Immunopathology and oligoclonal T cell expansions. Observations in immunodeficiency, infections, allergy and autoimmune diseases. *Curr Trends Immunol* 2009; 10: 21-9.

DUAL CHAMBER PACING MODE WITHOUT AN ATRIAL LEAD CAN PRODUCE R-ON-T PACING AND VENTRICULAR FIBRILLATION

To the Editor:

In the article by Eyal et al. entitled "An unusual cause for ventricular fibrillation following cardiac arrest" [1], the authors report three episodes of ventricular fibrillation initiated by R-on-T pacing from "undersensing of the intrinsic electrical activity of the heart." While we agree that undersensing occurred, this undersensing and ensuing ventricular tachycardia likely resulted from a pacemaker inappropriately programmed to a dual chamber pacing mode in a patient with no atrial lead. This case reflects a commonly practiced, but truly unappreciated phenomenon that can result in patient injury or death.

Although the pacing device, its settings, and the lead configuration were not published, Dr. Marai (the corresponding author) kindly provided some additional information. He told us that they commonly use a dual chamber Medtronic 5388 temporary pacemaker, often set to DDD pacing mode, rate 70 bpm, AVd 170 or 180 msec, with only a ventricular lead.

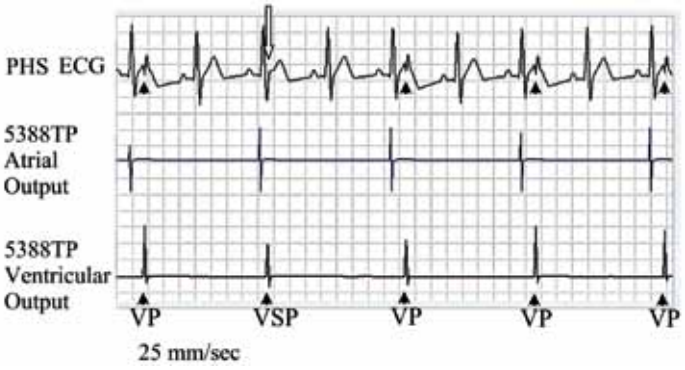

Figure 1. Temporary DDD pacing without an atrial lead produces R-on-T due to post-atrial-ventricular-blanking (PAVB). The top trace is the ECG output from a Medtronic proprietary patient heart rhythm simulator (PHS) set to: sinus rhythm, 1:1 AV conduction, 75 bpm (measured cycle length 813 msec), PR interval 200 msec. Only the PHS ventricular lead was connected to a Medtronic 5388 dual chamber temporary pacemaker (5388TP). The middle trace shows the atrial output from the 5388TP, and the bottom trace reflects the 5388TP ventricular output. 5388TP settings were: 60 bpm, AV delay 200 msec, V sensitivity 3 mv (PHS R waves 7–8 mv). Following a sensed R wave, the 5388TP emits an atrial pace at 800 msec, the VA time. The ensuing PAVB causes functional undersensing of the PHS ventricular event, and 5388TP emits a ventricular pace (VP) during the T wave (up-arrows on top trace) of the simulated patient. Note that the second 5388TP ventricular pace (VSP) was a "safety pace" with a short AV time and did not deform the "patient" QRS (open downward arrow). Not shown: Changing 5388TP to VVI mode eliminated the issue. However, changing 5388TP to DDI mode offered no protection, since VA time is unaffected. Making 5388TP more sensitive to ventricular events (i.e., V sens = 2 mv) produced predominantly 5388TP safety pacing, but T wave pacing continued to occur. [Reprinted from *Heart Rhythm* 2012; 9 (6): 970-3. Schulman PM, Stecker EC, Rozner M. R-on-T and cardiac arrest from dual-chamber pacing without an atrial lead. Copyright 2012 with permission from Elsevier].

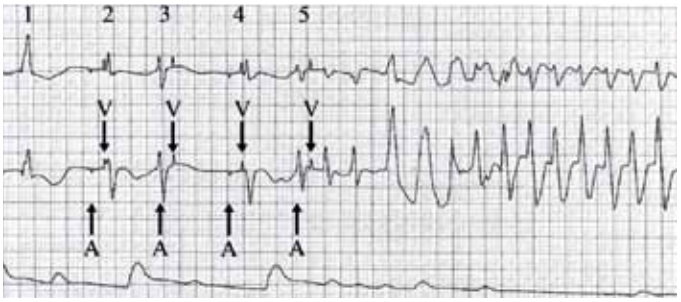

Figure 2. Normal dual chamber pacemaker timing can produce R-on-T pacing. Functional ventricular undersensing of a PVC with a resultant R-on-T pace initiated torsade-de-pointes. This patient had a dual chamber pacemaker in the DDD mode with a programmed lower rate of 70/min (R-R interval 857 msec) and AV delay 200 msec. With these parameters, the pacemaker will pace the atrium 657 msec after any previous ventricular event. A = atrial pacing, V = ventricular pacing. The top tracing is ECG lead II, the middle tracing is ECG lead V5, and the bottom tracing is the invasive arterial blood pressure. At approximately 660 msec after QRS#1 (which was appropriately sensed by the pacemaker), an atrial stimulus was emitted. At 200 msec following this atrial pace, a ventricular stimulus was emitted, appearing to depolarize the ventricle (QRS#2). About 660 msec later, the patient had a PVC (QRS#3). Because the pacemaker was preparing to emit the atrial stimulus it had disabled its ventricular sensing element and failed to sense this PVC (termed functional undersensing). At 200 msec following the atrial stimulus, no ventricular event had been sensed, so the pacemaker emitted a ventricular stimulus on the T wave. Because the ventricle was in a refractory period from the PVC, there was no depolarization of the ventricle (called functional non-capture). At 660 msec from this attempted V-pace, the pacemaker again paced the atrium, and it appears that the next V-pace captured the ventricle (QRS#4). At QRS#5, there is a repeat of the events at QRS#3: i.e.; the pacemaker disabled its sensing elements in preparation to pace the atrium and failed to detect the PVC. This time, however, the V-pace on the T wave initiated torsade-de-pointes. [Reprinted from Miller's Anesthesia, 7th edn. Miller RD, Fleisher LA, Johns RA, Savarese JJ, Weiner-Kronish JP, Young WL, eds. Rozner MA. Implantable cardiac pulse generators: pacemakers and cardioverter-defibrillators. Chapter 35: pp 1415-36, Copyright 2004 with permission from Elsevier].

As reported by Schulman et al. [2], dual chamber programming in the absence of an atrial lead can produce R-on-T pacing as a consequence of post-atrial ventricular blanking (PAVB). After expiration of the ventriculoatrial (VA) timer, a dual chamber pacemaker emits an atrial pace, then invokes PAVB to prevent ventricular output inhibition from cross-talk, thus preventing asystole in a pacing-dependent patient. With no atrial lead, no P wave will be sensed, so a pacemaker programmed to a dual chamber mode will "emit" this atrial pace and initiate PAVB. If this "phantom" atrial pace occurs simultaneously with a native QRS, then functional undersensing of the native QRS occurs because of PAVB. At the expiration of the AV time, a ventricular pace will be emitted which may fall on the T wave of the native QRS.

In the case presented by Eyal et al., the second R-on-T pace appeared about 150–200 msec from the QRS (without pacemaker markers the actual time of sensing cannot be determined), consistent with the reported AV delay. The first R-on-T pace occurred about 90–120 msec from the QRS, consistent with "safety pacing" that occurs when PAVB fails to blank the entire QRS.

Functional undersensing from dual chamber pacing without an atrial lead will take place whenever the native V-to-V interval exceeds a pacemaker's calculated VA time and occurs prior to the expiration of the PAVB [Figure 1]. The classic pattern is an R-on-T pace after every other QRS, since the QRS following a late V pace will occur prior to the expiration of the VA timer and no pacing will ensue. For dual chamber pacing at 70 bpm with an AV delay of 190 msec, the VA time is 667 msec (native rate 90). Their tracing is more consistent with pacing at 60 bpm, AVd 200 msec (VA time 800 msec, PAVB 20–40 msec), and an underlying sinus rate of 74 bpm (VV time 810 msec). In addition, R-on-T pacing can appear and initiate VT or VF despite appropriate programming in the setting of ventricular ectopy [Figure 2] or junctional rhythm [3].

We believe that dual chamber pacing without an atrial lead threatens patients and frequently creates R-on-T pacing with

the propensity for VT in cardiac surgery patients. Systems errors include use of the Medtronic 5388TP (probably the most common temporary external pacemaker) in a patient with an epicardial ventricular pacing wire but without a concomitant atrial wire, since the 5388TP automatically defaults to the DDD mode when activated. Finally, even when programmed to VVI, the 5388TP reverts to DDD pacing mode without warning with an accidental increase in the atrial output [4].

In summary, the ventricular undersensing resulting in R-on-T pacing and VF in this case likely resulted from an inappropriate (and default) DDD pacing mode in the absence of an atrial lead. The use of dual chamber pacing modes (DDD, DDI) in any patient without an atrial lead should be avoided.

M.A. Rozner PhD MD[1] and P.M Schulman MD[2]

[1]Dept. of Anesthesiology and Perioperative Medicine, University of TX MD Anderson Cancer Center, Houston, TX, USA and [2]Dept. of Anesthesiology & Perioperative Medicine, Oregon Health & Science University, Portland, USA [mrozner@mdanderson.org]

References

1. Eyal A, Adler Z, Boulos M, Marai I. An unusual cause for ventricular fibrillation following cardiac surgery. *IMAJ* 2013; 15 (5): 254-5.
2. Schulman PM, Stecker EC, Rozner M. R-on-T and cardiac arrest from dual-chamber pacing without an atrial lead. *Heart Rhythm* 2012; 9 (6): 970-3.
3. Rozner MA. Pacemakers and implanted cardioverter-defibrillators. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. 7th edn. New York: Churchill Livingstone/ Elsevier, 2009: 1387-409.
4. Schulman PM, Merkel MJ, Rozner MA. Accidental, Unintentional reprogramming of a temporary external pacemaker leading to R-on-T and cardiac arrest. *J Cardiothorac Vasc Anesth* 2013; 27 (5): 944-8 (2012 epub ahead of print).

RE: PARAPARESIS AND RHABDOMYOLYSIS

To the Editor:

The rare case reported by Benish and co-authors in a previous issue [1] recalled our four patients who developed an unusual clinical phenomenon of compartment syndrome with development of a flaccid paraparesis and rhabdomyolysis immediately after awakening from a prolonged sleep episode in an unusual posture (due to alcohol consumption and drug abuse). This could well be a 'new syndrome' [2].

Electrophysiological investigations were indicative of a sensory motor axonal-demyelinative polyneuropathy. All four patients were heavy smokers and two had subclinical hypothyroidism. Incomplete recovery was noted during the rehabilitation and follow-up period. Did our patients develop a syndrome that is a new entity, or do they resemble a coincidence of prolonged unusual posture followed by an acute onset of rhabdomyolysis, paraparesis and polyneuropathy?

The patients suffered from depressed mood, smoked cigarettes, consumed alcohol and/or drugs, and fell asleep in bizarre postures; what followed was a combination of rhabdomyolysis and compartment syndrome. Eventually they were diagnosed as having polyneuropathy and cauda equina syndrome.

Another case was described by a Croatian colleague, Dr. Pavao Vlahek [Personal communication, Croatian Physical Medicine & Rehabilitation Congress, 2012]. His patient was admitted with rhabdomyolysis and paraparesis after sleeping on the floor in an awkward position for 5 hours. He woke up with paraparesis. He was first admitted to an intensive care unit with high creatine phosphokinase levels (> 30,000 U/L) and treated for acute renal failure for 2 weeks and then sent to our ward where he started a rehabilitation program. It was assumed that he had a spinal cord injury after falling off the couch but there was no clinical or radiological evidence for this. This patient is a doctor who was active during the Croatian War in the 1990s. He was captured and spent a few months in a Serbian prison camp where he was tortured. It was presumed that at night he awoke, started to walk, and fell because he already had lower limb weakness.

A. Ohry MD

Dept. of Rehabilitation, Reut Medical Center, Tel Aviv, Israel [aohry@bezeqint.net]

References

1. Benish M, Zeitlin I, Deshet D, Beigel Y, Massive indoor cycling-induced rhabdomyolysis in a patient with hereditary neuropathy with liability to pressure palsy. *IMAJ* 2012; 14: 712-14.
2. Goldin D, Shemesh F, Eljashev-Shimshon R, Ohry A. A new syndrome sheds light on old medical and rehabilitative dilemmas: paraparesis due to rhabdomyolysis and bilaterally symmetric compartment syndrome in four patients. Cases study. *Ortop Traumatol Rehabil* 2010; 12 (6): 554-6.

Capsule

Topoisomerases facilitate transcription of long genes linked to autism

Topoisomerases are expressed throughout the developing and adult brain and are mutated in some individuals with autism spectrum disorder (ASD). However, how topoisomerases are mechanistically connected to ASD is unknown. King et al. found that topotecan, a topoisomerase 1 (TOP1) inhibitor, dose-dependently reduces the expression of extremely long genes in mouse and human neurons, including nearly all genes that are longer than 200 kilobases. Expression of long genes is also reduced after knockdown of *Top*1 or *Top2b* in neurons, highlighting that both enzymes are required for full expression of long genes. By mapping RNA polymerase II density genome-wide in neurons, the authors showed that this length-dependent effect on gene expression was due to impaired transcription elongation. Interestingly, many high confidence ASD candidate genes are exceptionally long and were reduced in expression after TOP1 inhibition. These findings suggest that chemicals and genetic mutations that impair topoisomerases could commonly contribute to ASD and other neurodevelopmental disorders.

Nature 2013; 501: 58

Eitan Israeli