Comparative and Evolutionary Medicine: An Example from Cardiovascular Medicine

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ABSTRACT

The application of comparative methods to clinical problems is well known to veterinarians. Physicians, to contrast, have poor awareness of the tremendous overlap in the pathology of animals and their human patients. They remain unexposed to the potential for comparative and evolutionary approaches to generate novel hypotheses and creative solutions to difficult human issues. Although the fields of human and animal medicine are moving closer together through One Health and related initiatives, most of the insights gained through these activities are in the areas of zoonoses, infectious diseases and public health. Physicians in other fields of medicine are largely unaware of the value of a comparative and evolutionary approach. Demonstrations of how comparative approaches can increase insights into human medical issues in non-infectious disease fields will help advance collaboration between a wider range of physicians and veterinarians. The power of a comparative and evolutionary approach to spark unique hypotheses is provided from the field of cardiovascular medicine. A common cardiovascular condition affecting people, vasovagal syncope (VVS), has non-human animal correlates and roots. Comparative analysis of VVS reveals insights into how and why this autonomic response occurs. This example provides a demonstration of how this perspective can enhance clinician understanding of high impact human concerns and spark new therapeutic approaches.

Keywords: One Health; Comparative Medicine; Cardiology; Vasovagal Syncope; Alarm Bradycardia

REVIEW

The application of comparative methods lies at the heart of the field of veterinary medicine. Given the range of species veterinarians encounter in clinical practice, comparative exposure is a crucial component of veterinary education and training. But the value of comparatively extends well beyond practical educational and clinical benefits. Applying a comparative perspective to any biomedical question can generate novel hypotheses and spark creative solutions to intractable challenges.

Unlike veterinary medicine, human medicine is *not* explicitly comparative. Physiology, pathophysiology and therapeutics are taught in reference exclusively to *Homo sapiens*. Most physicians are significantly unaware of the spontaneous occurrence of "human pathology" in non-human animals. This leads to the erroneous assumption among many physicians that many pathological conditions are uniquely human. This medical form of human exceptionalism not only deprives clinicians and physician-scientists of the hypothesis generating advantages of comparativity it obviates the possibility of using an evolutionary approach to understand the origins and etiology of pathological conditions. Recognition of the range of non-human animals in whom "human" pathology occurs helps expose the ancient roots of vulnerability to disease and can help illuminate the evolutionary origins of human pathologies.

One example of how comparative knowledge can enhance discovery comes from the field of cardiology. A comparative and evolutionary exploration of cardiac responses in a range of

wild species is helping to illuminate the origins of a common but puzzling clinical occurrence: vaso-vagal syncope (fainting).

Vaso-vagal syncope (VVS) is responsible for 3% of emergency room visits and 6% of hospitalizations (1, 2). One-third of all adults will have experienced VVS at least once in their lives. Syncope has several causes, many of them cardiac. Valvular heart disease, orthostatic hypotension and seizures may cause fainting. But it is vaso-vagal syncope which leads to more fainting than any other cause (3). Vaso-vagal fainting often occurs in the setting of extreme adrenergic activation. VVS has been reported with highly emotionally activating experiences including phlebotomy and the site of blood, watching the birth of a child, intense pain (i.e., long bone fracture), extreme fear or receiving extremely upsetting news (4, 5, 6). A specific autonomic reflex is responsible for emotionally activated VVS. The external event, fear, grief, and/or pain, triggers a robust adrenergic response (7). Instead of the expected fight/flight response with consequent tachycardia and vasoconstriction, a sudden withdrawal of sympathetic tone occurs which results in a parasympathetically-mediated bradycardia and vasodilation. This suite of autonomic responses results in a decrease in blood pressure with consequent reduction in perfusion to the central nervous system resulting in loss of consciousness (3).

Bradycardia in the face of adrenergically activating external circumstances, which include threat, seems counterintuitive. From an evolutionary perspective, a robust fight/flight response would seem to be vastly superior to the physiology of fainting. In fact, sympathetically-mediated fight/flight physiology *is* the more common autonomic response to external threat, fear or anguish.

But the withdrawal of sympathetic stimulation and consequent vagal dominance associated with VVS happens to nearly every human. The "heart drop" or woozy sensation after a career-jeopardizing mistake or a near-miss between your carful of kids and a truck, or stepping in front of a large audience results from this bradycardia-vasodilation response to external threat, pain, or anguish.

But why? What adaptive benefit might this seemingly paradoxical response have had in the ancestral environment in which our mammalian autonomic nervous systems evolved? Applying veterinary science, a comparative analysis and an evolutionary perspective sheds light on this question.

Do non-human animals exhibit a slowed heart rate and vasodilation responses to activating external stimuli? Do they ever faint? And if they do, then why? What adaptive benefit does this fainting physiology offer?

A comparative look at VVS begins to shed light on this question. External threat and fear trigger fight/flight responses in mammals, reptiles, birds and fish. But 'alarm bradycardia', the sudden reduction in heart rate in response to danger, fear, threat, is also found in the same broad range of non-human animal species (8, 9, 10, 11, 12, 13, 14, 15, 16). For example, white-tailed deer fawn responded to a variety of threatening stimuli with marked bradycardia (10). Similarly telemetry studies of the heart rates of willow grouse, woodchucks, rabbits and alligators have all demonstrated similar bradycardic responses to perceived threat (8, 9, 12, 13). The slowed heart rate associated with alarm bradycardia has been noted to be accompanied by reduced motion. This stillness generates the hypothesis that alarm bradycardia provides anti-predation protection for an animal when fight or flight responses are unlikely to be successful (14, 15, 16).

The epidemiology of alarm bradycardia and, in fact, VVS seems to support this hypothesis. Alarm bradycardia is strongest at the earliest phases of life, diminishing in intensity with age fight or flight responses become more dominant. White-tailed deer, for example, exhibit nearly exclusively bradycardic responses to threat in the first week of life. By the end of the first several weeks of life, however, they are much more likely to respond with sympathetically modulated flight responses. By 51 days of life, the response could not be elicited (10).

There are important comparative connections between alarm bradycardia in young animals and human populations. The sudden reduction in heart rate associated with VVS is also seen with greater frequency and intensity in young human life. One study published in 1993 looked at how the heart rate of soon-to-be born babies was affected by the sounding of sudden loud alarms. During the Gulf War in 1991, the calm of a labor and delivery ward in Israel was disrupted by the sounding of sudden loud alarms. Each woman had a fetal heart monitor around her abdomen which documented a dramatic plunge in fetal heart rates in response to the loud noise suggesting alarm bradycardia is present from the earliest stages of human life (17). The potency of this reflex in young vertebrates further supports the hypothesis that alarm bradycardia represents an anti-predation physiology. The youngest and most vulnerable of the species may lack the strength and/or speed to escape or fight their way out of danger. The acute slowing of the heart rate and

associated stillness represents a third survival strategy: staying quiet and still–hiding.

Through this veterinary and evolutionarily-informed analysis, VVS is not paradoxical at all. Rather, it represents an autonomic legacy that has been keeping animals safe for hundreds of millions of years.

Recognizing the linkage between alarm bradycardia and the bradycardia of VVS leads to potential therapeutic interventions. It appears, for example, that a decrease in the alarm bradycardic response is seen when animals are repeatedly exposed–and deconditioned–to the stress trigger. White-tailed deer fawn, for example, responded with alarm bradycardia to loud thunder only in the beginning of a storm. Successive thunderstorms failed to elicit the response (10). Perhaps a novel strategy to prevent syncope in a vulnerable population with recurrent VVS would be to develop deconditioning exercises targeting triggering stimuli. Or recognizing that juvenile animals appear to 'grow out' of this response as they age might help clinicians make challenging decisions about permanent pacemakers and other medical devices.

As evidenced by the above example, putting comparative knowledge into the hands of physicians allows for expanded and evolutionarily informed perspectives on common and enigmatic human pathologies. In the case of VVS the comparative analysis allows for the consideration of 'why' this autonomic response emerges under high stress conditions. It allows for a reframing of the traditional description of VVS as representing a paradoxical response to stress to one which points to an evolutionary past in which it was adaptive. This points to therapeutic strategies based on the syndrome being maladaptive rather than paradoxical.

Beyond the cardiovascular example offered above, the potential exists for comparative medicine to spark insights and have a transformational affect on many fields of medicine. The connection and overlap between veterinary and human syndromes is seen in fields ranging from psychiatry and pediatrics to neurology and nephrology. Bringing comparative perspectives to these and other fields of medicine will lead to expanded perspectives and novel hypotheses. One Health is an exciting idea which can and should span medicine in its entirety. Demonstrating how comparative and evolutionary insights do this in one field should provide a model for how it might be done in others. Given the longstanding and prominent place comparative medicine has had in veterinary science, veterinarians can and should emerge as leaders, teachers and innovators in developing effective initiatives to excite their physician colleagues about the power of a species-spanning approach to medicine. This collaborative approach will help physicians recognize the potential for effectively addressing medical challenges in people by paying close attention to the physiology and pathophysiology of non-human animals.

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