

Clinical perception and simple laboratory tests: do not mistake the finger pointing at the moon

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Submitted Jun 20, 2016. Accepted for publication Jun 20, 2016.

doi: 10.21037/atm.2016.06.31

View this article at: <http://dx.doi.org/10.21037/atm.2016.06.31>

Sometime in the past, in an urban emergency department (ED) of a large general hospital located somewhere around the globe, a patient entered the emergency room and asked to be seen by a doctor. He was a Caucasian male, aged around 62, smoker, with a history of type 2 diabetes, but not complaining for any particular symptom. He was simply “feeling bad”, thinking that he should be seen by a doctor. When the nurse completed the triage, and the patient was finally visited, he referred that same sensation of “feeling bad” to the emergency physician. As routine practice, the doctor ordered some first-line laboratory tests [a basic clinical chemistry profile, a complete blood cell count (CBC) and a cardiac troponin test] along with an electrocardiogram (ECG), to have a general picture of the health status. The test results, which were all available ~30 min afterward, revealed only two abnormalities. The value of cardiac troponin I (cTnI) was slightly above the 99th percentile of the assay (i.e., 52 vs. 36 ng/L), but still compatible with the age of the patient and the presence of diabetes (1). The only other abnormal finding was 19.0% of red blood cell distribution width (RDW), a value considerably higher than the upper limit of the reference range (i.e., 14.8%). The data emerged from the ECG were not suggestive for any typical cardiac disease, not the physical examination revealed meaningful issues. Yet, the patient insisted that he was feeling “bad”.

The emergency physician in care of the patient is a good friend of mine, and we have published a large number of studies about the clinical significance of RDW in many human pathologies. Despite the fact that no dramatically worrying sign had emerged as yet (beside the considerably increased RDW value), he was persuaded to refer the man to the catheterization lab, to have an angiography

performed. The patient was accommodated on a barrel and accompanied to the catheterization lab. Upon arrival to the interventional cardiology unit, which was located approximately 250 m from the ED, the patient had a sudden cardiac arrest. Over 15 minutes of reanimation efforts performed by the healthcare staff were ineffective. The patient died, approximately 1 hour after entering the ED. Two weeks later, the autopsy confirmed that the cause of death was a ventricular wall rupture secondary to a non-ST elevation myocardial infarction (NSTEMI), an exceedingly serious and deathly complication of myocardial infarction which may lead to cardiogenic shock and death in 30–50% of cases (2,3).

Some details of this story were modified to respect patient's privacy, but the sequence of the events in the ED and in the catheterization lab was real, dramatically true. Although really nothing could have been done (or even attempted) to change the fate of the poor man after he entered the ED, some take-home messages can be taken from the sad ending of this story.

One of the most distinguished emergency physician in Europe uses to say, “*When an elderly patient complains of feeling bad, you should start to seriously worry*” (4). Indeed, the lack of any precise sign of symptom should not be overrated, but it must still raise the alertness that something “systemically” wrong may be happening, and that the patient should be investigated rather than discharged for later assessment. The considerably increased RDW value was an additional and extraordinary sign in support that something really wrong was happening. We would all agree that a synthesis of intuition and analytical approach (i.e., “Gestalt” perception) remains one of the key elements of medical practice, laying at the heart of physicians’



Figure 1 Clinical perception and simple laboratory tests such as the red blood cell distribution width (RDW) can often guide the initial clinical decision making.

knowledge (5). The “Gestalt” is something that is hard to explain or simply bring back to visual, auditory, tactile or olfactory components. It is a kind of intuition originating from both personal inclination and experience. Indeed, “Gestalt” perception is not sufficient by itself, and should often be combined with results of diagnostic (either laboratory or imaging) testing for making a final diagnosis or for obtaining prognostic information. The many advancements in our understanding of biological pathways and the development of innovative diagnostic techniques (i.e., molecular testing, microarrays, sensitive and high throughput laboratory instrumentation) have generated a misleading perception that simple tests and human reasoning could be replaced by complex and multifaceted information emerging from panels of expensive biomarkers and resource-consuming techniques. That is a kind of mistaking the finger pointing at the moon. The RDW is a rather simple and inexpensive laboratory parameter, which reflects the degree of anisocytosis and thereby mirrors the heterogeneity of erythrocyte volumes (6). Many evidences accumulated in recent years suggest that this parameter, which is automatically calculated by all hematological analyzers and reported along with other parameters of the CBC, not only is strongly associated with a kaleidoscope of human diseases, but is also highly predictive of clinical

outcomes. As for the aforementioned case, RDW has been found to be a reliable diagnostic test for detecting myocardial infarction (7), but it does also independently predict major adverse cardiovascular events (MACE) and mortality in patients with an acute coronary syndrome (ACS) (8). The important information provided by the RDW is not limited to the boundaries of cardiovascular disease, but is much broader. Actually, an increased RDW value is currently regarded as one of the best predictors of mortality in the general population (9,10) as well as in critically ill patients (11,12). Despite the biological mechanisms underlying the association between RDW and human disease remain to be clearly defined, what is convincingly emerging from recent data is that anisocytosis should be considered an active player and not an innocent bystander, wherein the perturbation of erythrocyte biology seems to have a crucial role in the onset and progression of many human pathologies, such as cardiovascular disease, diabetes and cancer (13).

Despite the unhappy ending, the case of the 62-year-old man is a paradigmatic example of how the combination of clinical reasoning with simple and inexpensive (often neglected) laboratory tests may be an irreplaceable guide for the clinical decision making (*Figure 1*), inasmuch as technology should always be seen as an aid and not a surrogate of human reasoning (14). Confucius, an eminent Chinese teacher, editor, politician, and philosopher, said that often “...life is really simple, but we insist on making it complicated”. It is undeniable that rebirthing RDW will not revolutionize science and medicine, but I really hope that major focus placed by emergency physicians and general practitioners on underrated laboratory parameters such as the RDW may help saving more lives in the future.

Acknowledgements

The author is thankful to the emergency physician who played an active part in this case report, providing clinical and laboratory information.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Lippi G. Clinical perception and simple laboratory tests: do not mistake the finger pointing at the moon. *Ann Transl Med* 2016;4(16):299. doi: 10.21037/atm.2016.06.31