Title of review article: New technological devices for the assessment of systemic inflammation in the primary prevention of cardiovascular disease.

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Structured Abstract

Purpose of review: The prediction of cardiovascular disease events (CVD) is of strategic importance for the primary prevention of one of the big killers in the world. Predictive models have a history of decades, but still the desired accuracy is not reached by any of the existing models. The inclusion of inflammatory factors in the models did not increase their accuracy. In this review we discuss the possible reasons for that failure and we propose a paradigm shift.

Recent findings: Systemic inflammation is a very volatile phenomenon. The blood concentration of inflammatory biomarkers may change considerably in one individual with a timescale of seconds. Sudden changes in environmental conditions can trigger rapid modifications in the inflammatory profile of an individual. In routine clinical practice, the blood tests for inflammation are carried out at one point in time, not in standard environmental conditions, and are therefore inadequate.

Summary: We have to direct CVD research towards the understanding of the synchronic relationship between external environmental conditions and internal physiological reactions. CVD risk assessment must be carried out by using continuous real-time monitoring of external and internal parameters together, something that may become possible with the advent of new technological devices.

Keywords (MeSH): Inflammation; Biomarkers; Allostasis; Risk Assessment; Equipment and Supplies.

Abbreviations

CVD – Cardiovascular Disease

CRP – C-Reactive Protein

SES – Socioeconomic Status

OR – Odds Ratio

CI – Confidence Interval

SD – Standard Deviation

HS-CTnT – High-Sensitivity Cardiac Troponin T

Introduction

The prediction of cardiovascular disease events (CVD) is of strategic importance for the primary prevention of one of the big killers in the world. Predictive models have a history of decades, but still the desired accuracy is not reached by any of the existing models.

CVD is nowadays defined as an inflammatory condition sustained by the active communication between key cells, tissues, and organs, in contrast to the former definition of a passive accumulation of insults, such as high blood cholesterol, high blood pressure, smoking, and other conventional risk factors. Inflammatory processes participate in all stages of heart disease: initiation and evolution of atherosclerosis, plaque ulceration, thrombus formation, over-activation of the sympathetic neurohormonal axis, and coronary spasm.(1–5)

There have been attempts to use markers of systemic inflammation to improve risk assessments.(6,7) As yet, these attempts have not led to a consensual inclusion of any of these

biomarkers, and the risk score equations currently recommended by international clinical guidelines are based on the traditional risk factors for CVD.(8,9) One of the most convincing evidence of that failure came from a meta-analysis of data from 52 prospective studies that included about 250,000 participants without a history of CVD. The authors of that study investigated the value of adding C-reactive protein (CRP) or fibrinogen levels to conventional risk factors for the prediction of cardiovascular risk and calculated measures of discrimination and reclassification during follow-up, and modelled the clinical implications of initiation of statin therapy after the assessment of CRP or fibrinogen. The authors concluded that under current treatment guidelines, assessment of the CRP or fibrinogen level has minimal benefit and it is not of practical use, as they estimated that the inclusion of those inflammatory factors in the prediction could help prevent one additional event over a period of 10 years for every 400 to 500 people screened.(7)

Chronic psychosocial stressors such as anxiety and depression are able to evoke systemic inflammation (10–12) and are associated with heart disease with an effect size that is comparable to that of the traditional risk factors such as high blood pressure, cholesterol, smoking, etc.(11,13–15) For example, in a perspective study on 875 CVD patients followed up for 9 months, those with type D personality (chronic stress) had five times the odds of myocardial infarction or death compared with non-type D patients (odds ratio [OR] = 5.3, 95% confidence interval [CI] = 2.1 to 13.7) after adjusting for all other variables, including the traditional CVD risk factors and socioeconomic status (SES). The OR for smoking was 1.2 (95%CI = 0.47 to 3.0; P = 0.71).(16) Although the mechanisms involved in these complex pathways of causation have yet to be clarified genetically and phenotypically, there have been attempts to add markers of stress when performing cardiovascular risk assessments.(6,17–20) As yet, also those novel markers failed to add substantial predictive accuracy to the equations based on the traditional risk factors for CVD.(7–9)

It has been argued that the linear, monophasic approaches used to explain these mechanisms are not appropriate, and that “until a paradigm shift is adopted, cardiovascular biomarker research may

remain fascinating but probably unhelpful to medical practice and public health".(6) In this review we discuss the possible reasons for that failure and we propose a paradigm shift.

Allostasis

The notion of allostasis has drawn attention to the complex system of neuroendocrine responses to environmental challenges that is characteristic of living organisms. It has been conceptualised as the process through which organisms actively adjust to both predictable and unpredictable external events through the anabolism and catabolism of mediators, i.e. the way in which they maintain stability through change.(21) From this perspective, serious pathophysiology may occur when chronic overload resulting from sustained stress stimulates prolonged allostatic actions that in the long term lose their effectiveness and ability to respond.(22) The allostatic model suggests that sustained load is characterised by changes in the morphology of responses that are manifest in chronically-heightened basal levels, inadequate biological responses (blunted stress reactivity), and impaired post-stress recovery.(23)

In clinical and research settings, chronic systemic inflammation is flagged using single blood tests for inflammatory biomarkers, such as fibrinogen, C-reactive protein, and others. However, laboratory-based trials on humans(24) showed that the plasma concentration of inflammatory factors can change very rapidly following acute environmental changes such as stressful events (<1min). The average fibrinogen increase in response to the stress tasks was 5.1% (standard deviation [SD] = 7.3) with values ranging from −30.5% to +57.6% (therefore for some individuals fibrinogen plasma concentration decreased in response to the stress). The average increase in the lowest, middle, and top tertile was −1.9% (s.d. = 5.1), +5.0% (SD = 1.4) and +12.2% (SD = 5.8) respectively.(24) The artificial mental stress that was induced to those study participants mimicked the brief and mild types of stress that everyone encounters on a daily basis (or even hourly) during ordinary life. It is therefore arguable that the concentration of inflammatory biomarkers in the blood may have a

physiological continuous oscillation. Such instability affects the appropriateness of using a single blood test to flag a chronic systemic inflammation. Furthermore, there is a counterintuitive association between baseline inflammation and the extent of inflammatory reaction to acute stress: people with low baseline inflammation in their blood plasma have sharp and high inflammatory responses to acute stress, and this phenotype “A” is associated with low cardiac risk. Conversely, people with higher baseline inflammation have blunted and lower inflammatory responses and present higher cardiac risk (phenotype “B”).(24) Those dynamics make blood tests for inflammation further difficult to interpret. This complex non-linear association between mental stress and acute inflammatory response may be the reason why the use of single blood tests for inflammatory biomarkers does not have any practical utility in clinical activity or in public health policy making. Figure 1 shows an explicative diagram of the association between acute stress and acute inflammatory response. As an example, a one-off test for plasma fibrinogen that resulted in a concentration of 320 mg/dL would be compatible with both high and low chronic inflammation and with both high and low risk for CVD. Therefore, single tests for inflammation may have failed to add any accuracy to predictive models because the interpretation of those test results may vary due to an individual's exposure to environmental conditions such as psychosocial stress (either an unhealthy chronic exposure or a healthy acute exposure). A finding of elevated inflammation might be an indicator of chronic elevation due to chronic psychosocial stress but also an indicator of a healthy acute response to a recent acute stressful event. In other words, a finding of elevated inflammation would be clinically unfavourable only if it is coupled with chronic psychosocial stress, and favourable if it is due to a healthy stress response in an individual with good psychosocial adaptation. These complex dynamics have been further studied using measures of chronic stress.(25) The interference (effect modification) of chronic stress in the association between test results for inflammation and CVD risk has been explicitly assessed using multiplicative models. The results from those studies confirmed that a single test result of elevated inflammation might be associated with higher risk of cardiac disease only when it is accompanied with chronic

environmental (psychosocial) strain.(25) The interaction effect is reciprocal: not only a test finding of elevated inflammation is associated with higher CVD risk only when chronic stress is present, but also reported chronic stress is associated with higher CVD risk only when inflammation is present. That interaction may explain why inflammation and chronic stress failed to add accuracy to predictive models: each of the two variables is a weak predictor of CVD when it is assessed in isolation, and it is a null predictor when the estimate is adjusted for the other variable. The solution for this problem seems to be obvious: predictive models must explicitly allow for this interaction using interaction parameters between the covariates. However, we will see that this approach has severe limitations too.

Statistical limitations

Acute inflammation, chronic inflammation, acute psychosocial stress, chronic psychosocial stress, are umbrella terms for a range of blood tests, indicators, markers, or questionnaires that are interconnected within each domain, and each indicator measures different but often related aspects of each phenomenon. All tests used to mark any of those conditions are imperfect and there is no gold-standard reference.

For example, inflammation is possible thanks to the communication, the interaction, and the aggregation of different cell types. That communication is made possible by chemical signals called cytokines, which are small, non-structural proteins with molecular weights ranging from 8 to 40,000 Dalton. Nearly all nucleated cells are capable of synthesizing these proteins and, in turn, of responding to them. There is no aminoacid sequence motif or three-dimensional structure that groups cytokines. Some cytokines act to promote inflammation (pro-inflammatory), whereas others serve to reduce inflammation (anti-inflammatory) with a very complex network of reactions.(26) We nowadays delve into such complexity, but the explanation of the cell-signalling networks involved in inflammation is still an unsolved enigma.(27) As a consequence, clinical and epidemiological studies

typically measure all available inflammatory markers with the aim of increasing the probability of positive findings and often recode their test results or combine them into scores to seek the best statistical evidence.(28,29) This approach might be useful for developing predictive models, but it is at elevated risk of false positive findings due to random error and, even more worryingly, it has no clinical meaning. In clinical practice, inflammatory markers are too non-specific to be a useful tool for diagnosing or predicting serious underlying disease and should rarely be used in this situation.(30) In an incidental finding of raised levels of inflammatory markers, if history and examination yield no clues as to cause, it is reasonable to wait and see if symptoms develop.(30)

For mental stress the situation is not less complicated than for inflammation. In the following paragraph we report an incomplete list of stress indicators that have been used for epidemiological and clinical studies, schematically divided into three main themes, i.e. chronic stressors, mood factors, and social relationships:(31)

1. Chronic psychological distress
    a. Work stress
        i. High-demand/low-control
        ii. Effort-reward imbalance
    b. Family conflicts and care giving
    c. Low emotional support
    d. Financial strain
2. Mood and behavioural factors
    a. Depression
    b. Anxiety
    c. Hostility and anger
    d. Optimism
    e. Positive thinking

f. Hopelessness/Helplessness

3. Social relationships
    a. Social cohesion
    b. Social support
    c. Social network
    d. Neighbourhood problems

The above conditions do not have well-defined boundaries and hence each condition can be pertinent to more than one theme. Factors such as job strain, social network, and others can be measured objectively - even though they are often measured by self-report - and can therefore mark someone's objective exposure to stress, whereas some other factors such as depression, anxiety, and others are rather subjective mental representations, and can be thus considered as markers of individual response and adaptation to stress. Mental stress is therefore a multi-dimensional concept and can be considered as a subjective state as well as a biological phenomenon.(32)

In summary, although both inflammation and stress are associated with CVD and may be included in predictive models, they do not have gold-standard measures. All their indicators are far from being accurate. This inaccuracy brings in considerable information bias with consequent dramatic reduction in the predictive power of the statistical models. Although we have suggested that interaction parameters between the two factors would greatly improve the models, the inevitable measurement errors coupled with the low power of the interaction tests would make the effort unfruitful, and it would be impossible to provide public health policy makers or clinicians with a valid tool for risk assessment using such models.

Recommendations for future research

Future research has to diverge from its current focus and go in two opposite directions compared with where it is placed at the moment. The current focus lies in the middle between the study of the

biological mechanisms of inflammation and the study of clinical disease prevention. From the one hand, we must go backwards and disentangle the early dynamics of inflammation in basic biological studies to be carried out in vivo. This can be done by acknowledging and focusing on the complex interactions between mind and body. We must develop prototypes of instruments that would able to measure the synchronic association between inflammation and mental stress in vivo in a continuous way, something analogous to the Holter test for blood pressure or the exercise electrocardiogram, which would also record blood parameters, external events, and mental reactions (anxiety, irritability, depression, etc.) in real time. From the other hand, we must move forward along the causal pathways leading to CVD events and identify more proximal precursors of CVD in order to be able to develop adequate predictions. Cardiac troponin may be a good candidate for that purpose.

Cardiac troponin is a protein operating within the heart muscle cell, where it regulates the contractile activity. During a heart attack these cells rupture and troponin is released into the main blood stream; troponin can be detected in the peripheral venous blood as a specific marker of cardiac damage as it is normally present only in the cardiac muscle. Cardiac troponin is currently the gold standard biomarker for diagnosing patients with heart attack in hospitals.(33) High-sensitivity assays have recently been developed and the troponin subunit T (HS-CTnT) has shown the highest epidemiological sensitivity in hospital settings.(34,35) With the advent of high-sensitivity assays, troponin positivity has become a common finding even in individuals not displaying symptoms of heart disease or any other acute or chronic condition, possibly due to leakage through the membranes of partially-damaged heart cells or due to some other unknown mechanism.(36) In the general population, HS-CTnT positivity is associated with greater subsequent incidence of heart disease and mortality and can therefore be considered as the most proximal sentinel marker of heart disease and an index of cardiac health.(37,38) It is possible to estimate cardiac risk at a population level using this marker.(38–40) It was found that HS-CTnT blood concentration is

sensitive to inflammatory factors and to their complex interactions with environmental conditions such as acute and chronic psychosocial adversity in healthy people.(12,24,25,41,42) Therefore, since HS-CTnT is associated with augmented risk of CVD events and it is an objective and valid blood test that incorporates and integrates the effects of chronic inflammation and of psychosocial adversity along those of the traditional risk factors for CVD, (12,24,25,42) it is likely that a risk score equation including HS-CTnT as a predictor variable may provide valuable complementary information that could be added to clinical practice and to existing predictive methods.

Furthermore, the traditional risk score equations aim at predicting CVD events within 10 years from the prediction (i.e. with a time-resolution of 10 years). This is due to the fact that abnormalities in the factors traditionally measured (e.g. high blood pressure and cholesterol) take a long time to damage the arteries and to predispose to CVD events. HS-CTnT positivity is a much more proximal factor to CVD and therefore by using this new biomarker we may become able to predict CVD events in a shorter term, e.g. at 1-3 years. Short-term predictions are usually more accurate and also more useful than long-term ones. The incorporation of HS-CTnT in risk score equations will likely reduce the NNT (number-needed to treat).

Conclusion

We have to direct CVD research towards the understanding of the synchronic relationship between external environmental conditions and internal physiological reactions. For the future, we envisage that CVD risk assessment will be carried out by using continuous real-time monitoring of external and internal parameters together, something that may become possible with the advent of new technological devices, in conjunction with proximal precursors of CVD including cardiac troponins.

Key-points

Systemic inflammation is a volatile phenomenon.

The environment can drive sudden changes in the inflammatory profile of an individual.

Single blood tests are not able to measure CVD-related systemic inflammation with adequate accuracy.

The association between systemic inflammation and cardiovascular disease must be studied using continuous real-time monitoring of external and internal parameters together.

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Figure 1. An example of the dynamic association between acute mental stress and fibrinogen reactivity in relation to risk of CVD.