PERSPECTIVE

Clinical implications of erectile dysfunction: a new paradigm in the investigation for cardiovascular risk

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The common pathology of vascular endothelium dysfunction in erectile dysfunction and cardiovascular disease provides opportunities for the use of erectile dysfunction as a marker and predictor for future atherosclerotic cardiovascular events.

Erectile dysfunction (ED), the consistent or recurrent inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual performance, is a commonly occurring age-related condition.[1-3] Previously branded as impotence and regarded as a lifestyle inconvenience associated with psychological factors, ED is now known to be multifactorial and mostly vasculogenic.[3-5]

The ED–CVD nexus

The close relation between ED and cardiovascular disease (CVD) has been well documented.[6] Men with cardiovascular (CV) risk factors such as obesity, diabetes mellitus, hypertension and dyslipidaemia (the clinical components of the metabolic syndrome) are at significantly higher risk for ED.[7-9] CV risk factors and CVD have also been found to be significantly more prevalent in men with ED, especially severe ED.[3,10]

This intimate nexus has evolved further with subsequent research evidence showing that atherosclerosis from dysfunction of the vascular endothelium is the common denominator in the pathophysiology of ED and CVD.[11] In both conditions, endothelial dysfunction is affirmed by increased plasma levels of biomarkers of systemic inflammation such as the proinflammatory cytokines interleukin-6, interleukin-8 and interleukin-18 as well as high sensitivity C-reactive proteins.[12] ED is thus very much a manifestation of generalised vascular endothelial disease in the penile vascular bed.

ED as a novel predictor for CV events

The findings from a recent linked-data study have brought forth yet another new dimension to the relation between ED and CVD.[13] In this study, the incidence rates of atherosclerotic CV events subsequent to ED in the various age

Key points

- **Erectile dysfunction (ED) is a novel marker and predictor for future atherosclerotic cardiovascular (CV) events and death due to CV causes.**
- **Atherosclerosis resulting from dysfunction of the vascular endothelium is common to both ED and CV disease (CVD).**
- **Atherosclerotic changes are likely to be evident earlier in arteries of smaller calibre, such as those in the penile vasculature, than in the larger arteries of the coronary circulation.**
- **In spite of their increased risk of death due to CV causes, almost as many men with ED die from cancers as from CV causes, and these cancer deaths occur sooner.**
- **Rigorous investigation of men with ED provides information on their individual CV risk and opportunities for its early minimisation.**

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groups of a cohort of men with ED were compared with the corresponding incidence rates in a sample of men from the general population. The standardised incidence rate ratio (IRR) of 2.2 (95% CI 1.9 to 2.4) indicates that ED is significantly associated with subsequent atherosclerotic CV events. As the findings in the study were based on hospital admissions and death registrations, and the reported CV events had therefore necessitated inpatient management or eventuated in death, these findings signify an increased risk of CV events at the severe end of the spectrum of CVD.

Furthermore, although vasculogenic ED is more commonly seen in older men because CV risk factors become more prevalent as age advances and the absolute numbers of CV events in the study increased with age, the IRRs for subsequent atherosclerotic CV events were more than seven times higher in men under 40 years of age than the IRRs in men aged 70 to 79 years. This suggests that the predictive value of ED for subsequent CV risk is higher in younger men. As almost half of sudden cardiac deaths are known to occur in patients with silent coronary artery disease, the finding from the study that about a quarter of the deaths from CV causes had occurred with no records of hospital admissions for CVD also raises the possibility that these deaths had occurred without warning from asymptomatic CVD.[13,14]

All these findings are consistent with the postulate of the 'artery-size' hypothesis, which suggests that atherosclerotic changes are likely to be evident earlier in arteries of smaller calibre, such as those in the penile vasculature, than in the larger arteries of the coronary circulation.[15] They engender a paradigm shift in the clinical implications of ED and foster ED as a novel marker and predictor for future atherosclerotic CV events.[13]

Atherosclerosis from dysfunction of the vascular endothelium is the common denominator in the pathophysiology of ED and CVD

ED and CVD mortality

Analyses of the linked-data study was expanded to examine the risk of CVD mortality in men with ED.[16] Compared with the reference population, men with ED were at significantly higher risk of death from CV causes, with a standardised mortality rate ratio of 2.2 (95% CI 1.6 to 3.0). The finding that the increased risk was seen in men with ED aged 40 to 69 years and not in the oldest age group suggests that, as in the case of subsequent CV event, the predictive value of ED for CVD mortality is decreased in the older person.

In spite of the significantly increased risks of subsequent CV events and of CVD mortality, however, only 35.4% of the deaths that had occurred in the study cohort of men with ED were deaths from CV causes, whereas 28.9% were deaths from cancers, notably cancers of the respiratory, gastro-intestinal and genitourinary tracts. In addition, compared with the CV deaths, a greater proportion of the cancer deaths occurred within five years of the manifestation of ED (10.8% and 25%, respectively). These findings suggest that, in spite of the increased risk of CV death, almost as many men with ED die from cancers as from CV causes and that these cancer deaths occur sooner.[16]

ED, testosterone levels and CVD

Of late, age-related decline in blood testosterone levels and testosterone deficiency from other causes have emerged as new parameters of risk for CVD. In addition to being associated with insulin resistance, metabolic syndrome and diabetes mellitus, low blood testosterone levels have been linked to increased risk of CV events and increased CVD, cancer and all-cause mortality.[17-19] Although appropriate endocrine evaluation should be a part of the investigative protocol in men with ED, the possibility of reverse causation must be considered in interpreting blood testosterone levels when coexisting morbidities are present, and a diagnosis of testosterone deficiency should only be made according to established guidelines.[20] Decreased blood testosterone level is an infrequent cause of ED, and improved sexual functions from testosterone therapy are seen only in hypogonadal men.[21,22]

Clinical implications of ED

CVD is the leading cause of death and of morbidity in Australia.[23] Even if CV death is neither inevitable nor imminent because of the beneficial outcomes in terms of slower disease progression and longer patient survival from improved management of CVD, the relevance and importance of careful CV risk evaluation cannot be over-emphasised. The known association of cigarette smoking with ED, CVD and cancers is additional compelling rationale for proactive action.[23-25]

Research on the relation between ED and CVD has provided a new paradigm in the investigation for CV risk. The rigorous investigation of men presenting with ED, particularly younger men and men with a history of cigarette smoking, provides clinicians with opportunities to identify and minimise CV risk if this is present when CVD is silent or asymptomatic. CT

References

A list of references is available on request to the editorial office.

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References

1. NIH Consensus Development Panel on Impotence: Impotence. JAMA 1993; 270: 83-90.
2. Lewis R, Hatzichristou D, Laumann E, McKinlay J. Epidemiology and natural history of erectile dysfunction: risk factors including iatrogenic and aging. In: Jardin A, Wagner G, Khoury S, Giuliano F, Padma-Nathan H, Rosen R, ed. Erectile dysfunction. Plymouth, UK: Health Publications Ltd; 2000. p.19-51.
3. Chew KK, Stuckey BGA, Bremner A, Earle C, Jamrozik K. Male erectile dysfunction: its prevalence in Western Australia and associated sociodemographic factors. J Sex Med 2008; 5: 60-69.
4. Feldman HA, Goldstein, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study.
J Urol 1994; 151: 54-61.
5. Shabsigh R, Anastasiadis AG. Erectile dysfunction. Ann Rev Med 2003; 54: 153-168.
6. Chew KK, Bremner A, Earle C, Jamrozik K, Stuckey BGA. Male erectile dysfunction and cardiovascular disease: is there an intimate nexus? J Sex Med 2007; 5: 928-934.
7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005; 112: 2735-2752.
8. Matfin G, Jawa A, Fonseca VA. Erectile dysfunction: interrelationship with the metabolic syndrome. Curr Diab Rep 2005; 5: 64-69.
9. Demir T, Demir O, Kefi A, Comlekci A, Yesil S, Esen A. Prevalence of erectile dysfunction in patients with metabolic syndrome. Int J Urol 2006; 13: 385-388.
10. Chew KK, Earle CM, Stuckey BGA, Jamrozik K, Keogh EJ. Erectile dysfunction in general medicine practice: prevalence and clinical correlates. Int J Impot Res 2000; 12: 41-45.
11. Watts G, Chew KK, Stuckey BGA. The erectile-endothelial dysfunction nexus: new opportunities for cardiovascular risk prevention. Nat Clin Pract Cardiovasc Med 2007; 4: 263-273.
12. Giugliano F, Esposito K, Di Palo C, et al. Erectile dysfunction associates with endothelial dysfunction and raised proinflammatory cytokine levels in obese men. J Endocrinol Invest 2004; 27: 665-669.
13. Chew KK, Finn J, Stuckey B, et al. Erectile dysfunction as a predictor for subsequent atherosclerotic cardiovascular events: findings from a linked-data study. J Sex Med 2010; 7: 192-202.
14. Deedwania PC. Asymptomatic myocardial ischemia.
In: Crawford MH, DiMarco JP, Paulus WJ, eds. Cardiology.
St Louis, MO: Mosby; 2004. p. 285-296.
15. Montorsi P, Ravagnani PM, Galli S, et al. The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. Am J Cardiol 2005; 96: 19M-23M.
16. Chew KK, Gibson N, Sanfilippo F, Stuckey BGA, Bremner A. Cardiovascular mortality in men with erectile dysfunction: but not inevitble. J Sex Med. 2011 Mar 11. doi:10.1111/j.1743-6109.2011.02239.
17. Yeap BB. Androgens and cardiovascular disease. Curr Opin Endocrinol Diabetes Obes 2010; 17: 269-276.
18. Kaushik M, Sontineni SP, Hunter C. Cardiovascular disease and androgens: a review. Int J Cardiol 2010; 142:
8-14.
19. Jones TH. Testosterone deficiency: a risk factor for cardiovascular disease? Trends Endocrinol Metab 2010; 21: 496-503.
20. Conway AJ, Handelsman DJ, Lording DW, Stuckey B, Zajac JD. Use, misuse and abuse of androgens. The Endocrine Society of Australia consensus guidelines for androgen prescribing. Med J Aust 2000; 172: 220-224.
21. Earle CM, Stuckey BGA. Biochemical screening in the assessment of erectile dysfunction: what tests decide future therapy? Urology 2003; 62: 727-731.
22. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol 2005; 63: 381-394.
23. Australian Institute of Health and Welfare (AIHW). Australia's health 2008: the eleventh biennial health report of the AIHW. Cat. no. AUS 99. Canberra: AIHW; 2008.
24. Chew KK, Bremner A, Stuckey BGA, Earle C, Jamrozik K. Is the relationship between cigarette smoking and male erectile dysfunction independent of cardiovascular disease? Findings from a population-based cross-sectional study.
J Sex Med 2009; 6: 222-231.
25. Shopland DR, Eyre HJ, Pechacek TF. Smoking-attributable cancer mortality in 1991: is lung cancer now the leading cause of death among smokers in the United States? J Nat Cancer Inst 1991; 83: 1142-1148.