New frontiers in heart failure detection: saliva testing

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INTRODUCTION
Cardiovascular disease (CVD) covers a broad range of health conditions that affect the heart and blood vessels. The most common CVDs include coronary heart disease (CHD), ischaemic heart disease (IHD), acute myocardial infarction (AMI), stroke and heart failure (HF). This commentary will focus on the use of saliva to detect HF. HF is a complex pathophysiological syndrome that arises due to the inability of the heart to take in and/or supply sufficient blood to the body. The clinical manifestation of HF could arise due to myocardial disease, most commonly coronary artery disease, hypertension and cardiomyopathy. Even though the aetiology of HF is highly variable, HF syndrome represents the interplay between the cardiac, renal and vascular systems.

With an ageing and a growing population, the worldwide incidence of HF is predicted to increase in the coming years. HF affects 23 million people worldwide. Hospital admissions due to HF in the USA are >1 million per year, with an estimated cost exceeding US$39 billion annually. The population estimate of HF prevalence varies between 2% and 10%, depending on the population. The prevalence rates may be higher in selected population groups such as people suffering from morbid obesity, type 2 diabetes, hypertension, myocardial ischaemia and chronic kidney diseases. About 50% of people with left ventricular dysfunction are asymptomatic, undiagnosed and, as such, presumably untreated. Current therapies can treat asymptomatic and symptomatic left ventricular dysfunction. and the treatments are more effective earlier in the disease onset. Consequently, strategies aimed at early detection and early intervention represent a far more cost-effective approach, reducing the progression of HF in an individual and thereby reducing the societal impact. However, currently, there are no screening tests being broadly utilised on population groups at risk of developing HF.

Screening for HF in high-risk individuals will allow earlier intervention, thereby improving quality of life and survival rates. In Australia, the SCREEN-HF longitudinal trial aims to recruit over 3500 individuals at risk of developing HF. The clinical outcomes from this study could outline screening strategies for HF. Multiple population-based screening strategies have been investigated, such as end point clinical parameters (signs and symptoms); ECG; cardiac biomarkers in body fluids and echocardiography. However, none of these methods have shown a clear cost-effective benefit when used alone.

There is increasing scientific evidence linking oral health to systemic diseases, such as CVDs, cancer, rheumatoid arthritis and osteoporosis, to name a few. This is an important connection in terms of preventing chronic disease and disability, and reducing healthcare costs. While associations between oral and systemic health can be made, and research is on the rise, specific cause-and-effect relationships remain elusive. The World Oral Health Report, in 2003, clearly stated that the relationship between oral health and general health is proven by evidence. Oral health and general health are inter-related in four different ways: (1) poor oral health is associated with major chronic diseases; (2) poor oral health causes disability; (3) common risk factors are shared between oral health and major diseases and (4) general health problems may cause or worsen oral health conditions. Research has also demonstrated that the association between oral inflammation and systemic inflammation may be the key to understanding how oral health is associated with general health. In light of these
aspects, it becomes prudent then to measure and analyse human saliva as an alternative medium to systemic events.

Salivary diagnostics holds great promise as an alternative biofluid to blood and urine for the early diagnosis, prognosis and monitoring of post-therapy status.\textsuperscript{16–20} Saliva is championed as the diagnostic fluid of the future over blood, as saliva testing is easy, inexpensive, safe and non-invasive.\textsuperscript{19} Whole saliva is a mixture of the secretions of the major and minor salivary glands, mucosal transudations, gingival crevicular fluid, serum and blood derivatives from oral wounds, desquamated epithelial cells, expectorated bronchial and nasal secretions, bacteria and bacterial products, viruses and fungi, and other cellular components.\textsuperscript{18} Saliva is a non-Newtonian complex biofluid consisting of hormones, proteins, enzymes, antibodies, antimicrobial constituents, DNA, micro RNA and messenger RNA, and cytokines. In other words, saliva can be referred to as the ‘plasma ultrafiltrate’.\textsuperscript{27} The transportation of biomolecules across blood endothelium into salivary acini cells may occur via transcellular, passive intracellular diffusion and active transport, or through paracellular routes by extracellular ultrafiltration via salivary glands or through the gingival crevice.\textsuperscript{28–29} The various biomolecular-transportation mechanisms between salivary acini cells and blood endothelium cells have been described in detail.\textsuperscript{13} 30 31

My team\textsuperscript{31} and others have detected and quantified cardiac tissue-specific proteins in human saliva. Examples include the quantification of N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) levels in saliva from patients with HF compared with healthy controls,\textsuperscript{4} 32 with no correlation between salivary and plasma NT-proBNP levels. Denver et al\textsuperscript{33} detected elevated levels of endothelin in patients with chronic HF and also demonstrated that salivary endothelin levels correlated with HF disease severity (through each New York Heart Association Functional Class).\textsuperscript{33} Elevated C reactive protein (CRP) levels were detected in saliva collected from patients with IHD\textsuperscript{34–37} compared with healthy controls. Punyadeera et al\textsuperscript{35} also demonstrated a positive and significant correlation ($r^2=0.84$, $p<0.001$) between salivary and serum CRP levels, indicating the potential clinical use of salivary CRP in detecting and possibly monitoring IHD. Papers by Mirzaii-Dizgah and Riahi,\textsuperscript{38} and Floriano et al\textsuperscript{39} have clearly demonstrated that cardiac troponin-T and troponin-I (a biomarker for myocardial necrosis), myoglobin (MYO), creatine kinase MB and myeloperoxidase, are datable in saliva of patients with AMI. They also found that the MYO levels were elevated in saliva within 48 h of onset of chest pain in patients with AMI, and noted a correlation between saliva and blood MYO levels. Furthermore, Mirzaii-Dizgah demonstrated that using both stimulated (mechanical and/or acid) and unstimulated saliva, there was a strong correlation with serum high sensitive cardiac troponin T levels ($r=0.415$, $p<0.023$; $r=0.466$, $p<0.021$, respectively). A separate study by Miller et al found that the concentrations of CRP, tumour necrosis factor $\alpha$ (TNF-$\alpha$), and matrix metalloproteinase 9 (MMP-9) in saliva were significantly higher in patients with AMI, and positively correlated with the serum concentrations. These studies clearly demonstrate the potential clinical utility of saliva.

**FUTURE PERSPECTIVES**

It is becoming evident that the use of saliva as an alternative diagnostic medium for the detection of HF and other CVD has gained scientific and clinical attention. The use of saliva in place of traditional biofluids is accelerated by its non-invasive, simple method of sampling. Despite these advances in the field, more research is required to understand the relevance and transportation of certain cardiac biomolecules into saliva and their correlation with blood; their physiological roles, if any, within the oral cavity, the lag time between saliva and blood, and the ability to use saliva as a medium to monitor HF. Further studies are warranted to make saliva diagnostics a reality in the future, so as to benefit people from developed as well as emerging economies. Earlier diagnosis and early intervention may be able to reduce the global HF disease burden.

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Dentistry and oral medicine (1)
Drugs: cardiovascular system (4)
Screening (epidemiology) (2)
Screening (public health) (2)
Ischaemic heart disease (1)
Diabetes (1)
Immunology (including allergy) (3)
Inflammation (1)
Hypertension (1)
Stroke (5)
Clinical diagnostic tests (4)
Connective tissue disease (1)
Degenerative joint disease (2)
Echocardiography (1)
Health economics (4)
Health policy (4)
Health service research (4)
Metabolic disorders (1)
Musculoskeletal syndromes (2)
Osteoporosis (1)
Radiology (2)
Rheumatoid arthritis (1)
Urological surgery (2)
Urology (2)
Health education (6)
Health promotion (7)
Obesity (nutrition) (2)
Obesity (public health) (2)

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