HEMOTAG

Portable, point-of-care left ventricular function diagnosis system

Cardiac Health in Diabetes Mellitus

The clinical need for Point-of-Care Left Ventricular Dysfunction assessment in patients with diabetes mellitus.

Diabetes mellitus [DM] affects over 33 million patients in the US alone[1] and in addition to its known deleterious metabolic effects, it's strongly associated with elevated risk for cardiovascular disorders. The term "diabetic cardiomopathy" was introduced in 1972[2] to encompass macrovascular and microvascular pathologies associated with Type I and Type II DM[3]. While Type I patients exhibit a higher prevalence for coronary heart disease and peripheral arterial disease, Type II DM patients are more likely to suffer from obesity, peripheral arterial disease, large artery atherosclerosis, arteriosclerosis and stroke[4].

Diabetes mellitus increases cardiovascular mortality risk of adult patients by a factor of 1.7[5]; the relative risk for cardiovascular disease morbidity and mortality in adults with DM ranges from 1 to 3 in men and from 2 to 5 in women compared to those without DM[6]. Importantly, the risk of progressing to life threatening heart-failure from asymptomatic left ventricular dysfunction is nearly 70% to 500% higher than in subjects with normal function[23]. These risks are also reflected in the healthcare expense: patient with DM incur medical expenditures ~2.3 times higher than non-diabetic persons would have, overall, DM is responsible for ~1/4 of all healthcare expenses in the US[7]. With $327bn annually and rising by 26% over 5 years the scale of the epidemic is staggering.

Primary care physicians and endocrinologists are increasingly aware of the association between diabetes and heart disease, and form the first line of defense in preventing heart disease in DM patients. Unfortunately, unlike the metabolic pathologies in chronic DM, hyperglycemia-induced damage to the microvasculature can occur without overt symptoms and is difficult to diagnose in an outpatient setting without access to the "gold standard" of echocardiogram. Standard tests such as blood pressure and weight gain are insufficient to identify developing left ventricle dysfunction, even specialized tests such as brain natriuretic peptide and 12-lead ECG compare sub-optimally against echocardiogram[8].

The HEMOTAG reader positioned on a patient in ambulatory care. The rechargeable, wireless device uses standard ECG electrodes. A 30 second reading is initiated by the clinician via the secure App and an audible notification indicates the successful transmission of the data to the HIPAA secured cloud. Patient-centric reports are generated automatically and transmitted to the authorized care team. In addition to their diagnostic value in developing an intervention strategy, the reports also allow the clinician to engage the patient in a conversation about cardiac risk profiles before symptoms are manifest.

In absence of unambiguous tests available in outpatient settings, clinicians have but two choices to prevent or delay the onset and progression of cardiovascular disease in their DM patients. One option is to aggressively control the metabolic disorder, monitor and observe HbA1c and increase pharmacological and behavioral intervention even in asymptomatic patients. This option is not ideal since it adds significant burden on the patient and sometimes can not be recommended due to the patient's polypharmacy state and reluctance to comply given the absence of manifested symptoms. In addition, reducing HbA1c below "safe thresholds" is challenging, especially in patients where DM was diagnosed late or where blood glucose level are not sufficiently controlled. Further, while HbA1c concentration is also strongly correlated with heart failure, there is no "safe threshold"; a 1% reduction of HbA1c reduced the risk of heart failure by 16% and 21% reduction in morbidity directly attributed to DM[11].

Additionally, clinicians face significant educational hurdles in asymptomatic patients and risk increased non-compliance with the treatment. A second option available to a clinician presented with an at-risk but asymptomatic patient is cardiologist referral, echocardiogram and possibly stress-echocardiogram. While this option would generate unambiguous results, it is rarely realistic given the high cost of echocardiogram and the time and cost burden on the patient. In fact, currently ~20% of patients do not actually follow a referral at all[10–12]. One can estimate that the non-compliance rate is even higher in younger and asymptomatic patients.

In echocardiogram-guided diagnostics, diastolic dysfunction alters the relationship between the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'), and how long it takes for filling of the ventricle to start after the ventricle relaxes (length of the mitral valve opening = MVO). Diastolic dysfunction is assumed when the E/e' ratio exceed 14 and have been reported as early markers of diastolic heart failure in Type 1 Diabetes[18] and Type 2 Diabetes[19]. Similarly, diastolic dysfunction alters the relationship between the Left-atrial volume index (LAVi) which quantifies the degree of atrial dilatation, and how long it takes to the end of ventricular systole (length of the Aortic valve closing = AVC). LAVi below 34 ml/m^2 is a crucial marker in the prediction of heart failure[13–15], especially in DM where atrial dilatation is implicated in the cardiac disease progression[16,17]. And while these markers together can give a comprehensive assessment of cardiac health in diabetic patients, their reliance on 2-D transthoracic doppler echocardiogram relegate them to the exclusive domain of cardiology clinics.

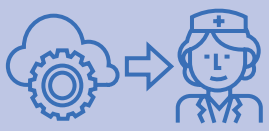
HOW HEMOTAG WORKS:

1. Patients with non-specific symptoms are evaluated in urgent or primary care settings. The device is easily and rapidly applied to the patient's chest.

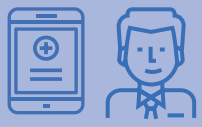
30
SECONDS

2. With the patient resting, the HEMOTAG app initiates the assessment. An audible signal indicates the end of the process.

90
SECONDS



3. HEMOTAG's HIPAA-compliant cloud uses machine learning algorithms to analyze the data and generate an electronic report.



4. The physician reviews the HEMOTAG report and assesses if a referral to a cardiologist is indicated or if heart function is normal.

2
MINUTES

Summarizing, DM patients are at higher risk for cardiac disease than non DM patients but neither primary care physicians nor endocrinologists have access to cost-effective, easy-to-operate but unambiguous cardiac function and anatomy systems to allow early diagnosis of asymptomatic heart disease. Clear diagnostic evidence of early heart disease would not only facilitate early therapeutic intervention but also allow a "teachable moment" with the patient while behavioral changes could still generate benefits.

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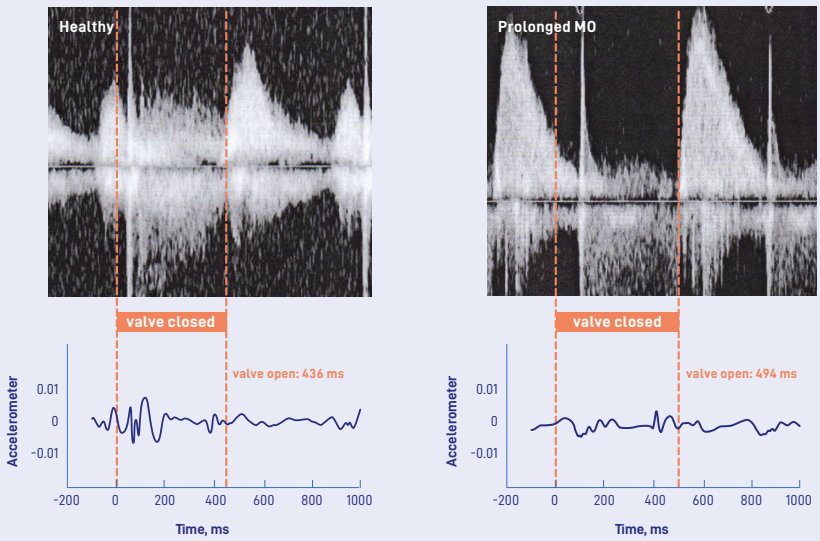
The Florida, USA based company Aventusoft worked with clinicians to fill this gap in cardiac diagnostic capability in a point-of-care setting. The requirements were to develop a self-contained device that can be used by a nurse or nurse practitioner, generates in-depth cardiac anatomical and functional data within the time-frame of a single consultation, automatically produces actionable reports and has an online component to allow data sharing with the patient's care team.

The HEMOTAG system achieves this by using a rechargeable, wireless sensor on the patient's chest that simultaneously records cardiac sounds from multiple angles at the same time. The high-resolution sounds allow identification of valves opening/closing and chambers filling/emptying and accurate measurements of the time intervals between the events. These time intervals are used to detect and report pathologies such as Left Ventricular Diastolic Dysfunction, one of the key cardiac risks in hypertension[20] and diabetes mellitus[21] that often remains asymptomatic until heart failure is manifest.

At the core, Aventusoft deployed its AI-supported algorithms developed with US military funding to detect transthoracically cardiac valve motions, and report cardiac valve time intervals that so far were in the exclusive domain of echocardiograms. Similar to echocardiogram in its diagnostic value but at a fraction of the price, the system was developed specifically to give primary care physicians and endocrinologist a robust, easy-to-use system at a price point comparable with blood pressure devices and the diagnostic value of a echocardiogram.

HEMOTAG (lower 2 traces) in comparison with conventional ECHO-cardiogram (top panels). Mitral-valve opening times (MVO) were calculated in control with E/e' = 10.9 (left panel) and a patient identified with left ventricular diastolic dysfunction with E/e' = 44.6 (right panel). Both systems generated comparable data proving that HEMOTAG can identify cardiac abnormalities in an outpatient setting without cardiologist support or prescription.



Summary

Diabetes mellitus is a chronic, progressive multi-factorial disease, challenging clinicians and their patients to view the impact of hyperglycemia on multiple organs. The slow, asymptomatic progression of diabetic cardiomyopathy is specifically difficult to control as diagnosis is generally conducted by cardiologists at a stage where pharmacological or even surgical intervention is indicated. Patients often do not see the need for further action due to the absence of debilitating symptoms, delaying preventative life-style changes or pharmacological treatment. Empowering the primary care team with unambiguous insights on the patient's cardiac health and delivering easy-to-understand reports to initiate teachable moments is the goal of the HEMOTAG CPAS.

Early diagnostic of developing cardiac pathologies allows the primary care team to plan and execute early interventions ranging from education and lifestyle changes to more robust monitoring of Hemoglobin A1C and blood glucose. HEMOTAG allows the diagnosis of cardiac pathologies within a single routine visit allowing the careteam a more integrated approach to manage the patient's overall health and preventing or delaying the onset of debilitating cardiac disease.

References

1. E. J. Benjamin et al., Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. Circulation. 135, e146–e603 (2017).

2. S. Rubler et al., New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am. J. Cardiol. 30, 595–602 (1972).

3. M. Lehrke, N. Marx, Diabetes Mellitus and Heart Failure. Am. J. Cardiol. 120, S37–S47 (2017).

4. J. Putaala et al., Diabetes mellitus and ischemic stroke in the young: Clinical features and long-term prognosis. Neurology. 76, 1831–1837 (2011).

5. "National Diabetes Statistics Report, 2017 Estimates of Diabetes and Its Burden in the United States Background" (2017), (available at https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf).

6. A. A. Rivellese, G. Riccardi, O. Vaccaro, Cardiovascular risk in women with diabetes. Nutr. Metab. Cardiovasc. Dis. 20, 474–480 (2010).

7. A. D. American Diabetes Association, Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 41, 917–928 (2018).

8. V. Madhok et al., The accuracy of symptoms, signs and diagnostic tests in the diagnosis of left ventricular dysfunction in primary care: A diagnostic accuracy systematic review. BMC Fam. Pract. 9, 56 (2008).

9. I. M. Stratton et al., Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 321, 405–12 (2000).

10. J. C. Byrd, M. A. Moskowitz, Outpatient consultation: interaction between the general internist and the specialist. J. Gen. Intern. Med. 2, 93–8.

11. C. B. Forrest, E. Shadmi, P. A. Nutting, B. Starfield, Specialty Referral Completion Among Primary Care Patients: Results From the ASPN Referral Study. Ann. Fam. Med. 5, 361–367 (2007).

12. A. Mehrotra, C. B. Forrest, C. Y. Lin, Dropping the baton: specialty referrals in the United States. Milbank Q. 89, 39–68 (2011).

13. B. Ristow, S. Ali, M. A. Whooley, N. B. Schiller, Usefulness of left atrial volume index to predict heart failure hospitalization and mortality in ambulatory patients with coronary heart disease and comparison to left ventricular ejection fraction (from the Heart and Soul Study). Am. J. Cardiol. 102, 70–6 (2008).

14. G. Oyku, P. Hulya, C. Ozlem, D. Nilgun, Assessment of left atrial function in patients with type 2 diabetes mellitus with a disease duration of six months. Cardiovasc. J. Afr. 29, 82 (2018).

15. D. A. Patel, C. J. Lavie, R. V Milani, S. Shah, Y. Gilliland, Clinical implications of left atrial enlargement: a review. Ochsner J. 9, 191–6 (2009).

16. M. K. Poulsen et al., Left Ventricular Diastolic Function in Type 2 Diabetes Mellitus. Circ. Cardiovasc. Imaging. 3, 24–31 (2010).

17. K. K. Kadappu et al., Changes in left atrial volume in diabetes mellitus: more than diastolic dysfunction? Eur. Hear. J. - Cardiovasc. Imaging. 13, 1016–1023 (2012).

18. T. J. Bradley et al., Early changes in cardiovascular structure and function in adolescents with type 1 diabetes. Cardiovasc. Diabetol. 15, 31 (2016).

19. G. Zoppini et al., The E/e' ratio difference between subjects with type 2 diabetes and controls. A meta-analysis of clinical studies. PLoS One. 13, e0209794 (2018).

20. M. Galderisi, Diagnosis and Management of Left Ventricular Diastolic Dysfunction in the Hypertensive Patient. Am. J. Hypertens. 24, 507–517 (2011).

21. S. Bouthoorn et al., The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: A systematic review and meta-analysis. Diabetes Vasc. Dis. Res. 15, 477–493 (2018).

22. Echouffo-Tcheugui, et al. (2016). Assessing the Risk of Progression From Asymptomatic Left Ventricular Dysfunction to Overt Heart Failure. JACC: Heart Failure. 4:4. 237-248

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