

# Pre-clinical Detection of Cardiac Dysfunction and Coronary Artery Disease in Essential Hypertension: An Update

Luigi P. Badano, NS Dhalla, Yomna Galal Elkilany\*, Sherif Baath Allah, Jaipaul Singh, Ram B Singh, Navin C Nanda, Baset Essawy and Jan Fedacko

<sup>1</sup>Professor and Consultant of Cardiology –SCU , Tanta University , Egypt

<sup>2</sup>University of Milano, Bicocca, School of Medicine and Surgery, Milano, Italy and Istituto Auxologico Italiano, IRCCS, Department of neural, Cardiac and Metabolic Sciences, Milano, Italy

<sup>3</sup>Institute of Cardiovascular Sciences St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, Manitoba, Canada

<sup>4</sup>American University of Sharjah, UAE

<sup>5</sup>RAK Medical and Health Science University, UAE

<sup>6</sup>University of Central Lancashire, Preston, UK

<sup>7</sup>Halberg Hospital and Research Institute, Moradabad, India

<sup>8</sup>Alabama University at Birmingham, AL., USA

<sup>9</sup>Al-Azhar University, Egypt and Transplant Research Center, Renal Division, Brigham and Women Hospital, Harvard Medical School, USA

<sup>10</sup>Kosice Medical University, Slovakia

## Abstract

Systemic hypertension (HTN) is a syndrome and it can induce other diseases and biochemical abnormalities, including stroke, coronary artery disease, heart failure (HF), obesity, kidney failure, glucose intolerance, dyslipidemia and even death. Epidemiological researches have established that HTN is a powerful contributor to major cardiovascular diseases. Hypertension is the single most important preventable cause of premature death in the Western world estimating at 20% of adult population. The quest to find effective treatment, both in terms of blood pressure control and prevention, such as heart attacks and strokes are still on-going. Although clinicians favor the diagnosis and treatment of hypertension in terms of diastolic blood pressure elevation and categorical cut of points, epidemiological data show important influence of systolic blood pressure and associated risk factors that contribute to atherosclerosis predicting clinical HF. Early detection of subclinical myocardial disease among hypertensive population is a holy grail of all cardiologists, but difficult when using the conventional echocardiography (CE). By comparison to CE, speckle tracking echocardiography (STE) is more specific obtaining longitudinal and circumferential strain, which are able to identify sub clinical myocardial abnormalities with a higher degree of accuracy. This review described the epidemiology of hypertension relating it to cardiovascular events including preclinical detection of cardiac dysfunction in HTN explaining how this could be detected by STE and other imaging modalities. These changes provide new targets for preclinical diagnosis monitoring responses to preventive strategies.

**Keywords:** Hypertension syndrome • Risk factors clustering • Hyperinsulinemia • Preclinical cardiac dysfunction • Echocardiography • Speckle tracking echocardiography

## Definition

High blood pressure or systemic hypertension (HTN) should be treated earlier with lifestyle changes and in some patients with medication – at 130/80 mm Hg rather than 140/90–based on new American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the detection, prevention, management and treatment of high blood pressure [1]. Blood pressure categories in the new guideline are: Normal BP is less than 120/80 mm Hg with elevated systolic pressure is between 120-129 mmHg and diastolic pressure is less than 80 mmHg. Stage 1 hypertension is when systolic pressure is between 130-139 mmHg and diastolic pressure is between 80-89 Hg. Stage 2 hypertension is when systolic pressure reaches at least 140 mmHg and

diastolic is elevated at least to 90 mm Hg. Hypertensive crisis is when systolic is elevated to over 180 mmHg and/or diastolic pressure is over 120 mmHg, with patients needing prompt changes in medication if there are no other indications of problems, or immediate hospitalization if there are signs of organ damage [1].

## Epidemiology of arterial hypertension:

Systemic hypertension (HTN) is a serious medical condition that significantly increases the risk of heart attack, stroke, kidney failure and blindness. It is one of the leading causes of premature death worldwide. Of the estimated 1.13 billion people who have hypertension, less than 1 in 5 have is under effective blood pressure control. The main contributors to the rise in hypertension are unhealthy diets, physical inactivity, stress, age, ethnicity, pregnancy, kidney failure and the consumption of alcohol and tobacco. To achieve the global target to reduce the prevalence of hypertension by 25% by 2025, WHO and the United States Centers for Disease Control and Prevention [2] launched the Global Hearts Initiative in 2016 with its five technical packages which include the followings: -HEARTS (manage cardiovascular diseases), MPOWER (control tobacco), Active (increase physical activity), SHAKE (reduce salt consumption) and REPLACE (eliminate trans-fat) – the Initiative aims to improve heart health worldwide. The HEARTS technical package itself gives guidance on more effectively detecting and treating people with hypertension in primary health care.

\*Address for Correspondence: Dr. Galaledin Nagib Elkilany, 132 Holly Drive, Laplace, LA, 70068. Tel: +971502777837 UAE/ +15044589224 USA; E-mail: galal@kilany.org / galal.elkilany@gmail.com.

**Copyright:** © 2021 Galaledin Nagib Elkilany, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Received** 22 December 2020; **Accepted** 12 January 2021; **Published** 19 January 2021

Globally, an estimated 26% of the world's population suffer from hypertension, and the prevalence is expected to increase to 29% by 2025, driven largely by increases in economically developing nations [2]. The high prevalence of hypertension exacts a tremendous public health burden and it is the primary contributor to heart disease and stroke which are the leading causes of death worldwide [3,4].

### High blood pressure and risk of cardiovascular events

The association between HTN and cardiovascular diseases (CVDs) is unequivocally established. The risk of cardiovascular events in the general population increases steadily with increases in arterial pressure. The individuals at greatest risk of suffering a cardiovascular event because of hypertension are those with the highest arterial pressures. However, mild to moderate hypertension is more common than severe hypertension, and much of the population burden of disease because of hypertension may be attributed to moderate rather than severe hypertension. Illustrated the effect of systolic pressure at entry to MRFIT (Multiple Risk Factor Intervention Trial) on the relative risk of death because of coronary artery disease (CAD). The number of excess deaths is calculated relative to the number of deaths because of CAD that would be expected from the death rate in the baseline group. The findings of MRFIT trial support recommendations, repeatedly made to the public by expert groups, for improved dietary/lifestyle practices (plus pharmacological treatment as needed) to prevent and control established major CAD/CVDs risk factors (dyslipidemia, hypertension, diabetes, overweight/obesity, related adverse eating practices, and smoking) [5].

The highest risk of death is seen in patients with systolic arterial pressures of greater than 180 mm Hg. However, those with systolic arterial pressures between 140 and 149 mm Hg are more common and are still at high risk of major cardiovascular events (MCVE). Hence, medical guidelines for the treatment of hypertension emphasize the treatment of mild to moderate hypertension.

Hypertension is quantitatively the most important risk factor for premature CVDs [6] and it is more common than cigarette smoking, dyslipidemia, and diabetes, which are the other major risk factors. Hypertension accounts for an estimated 54 percent of all strokes and 47 percent of all ischemic heart disease events globally [7]. This clustering is attributed to an insulin resistance syndrome promoted by abdominal obesity. Furthermore, the amount of risk factor clustering accompanying elevated blood pressure was observed to increase with weight gain. Based on the Framingham Study, data on the prevalence of insulin resistance syndrome (IRS) in the general population could be as high as 22% in men and 27% in women. In addition, the risk of CAD, the most common and most lethal sequel to hypertension, increased stepwise with the extent of risk factor clustering [8]. Moreover, hypertension increases the risk for a variety of CVDs [9, 10], including stroke, CAD, heart failure (HF), atrial fibrillation [11], and peripheral vascular disease (PVD).

The risk for both CAD and stroke increases progressively with incremental increases in blood pressure above 115/75 mmHg, as shown in numerous epidemiologic studies [7,12]. However, these observations do not prove a causal relationship, since increasing blood pressure could be a marker for other risk factors such as increasing body weight, which is associated with dyslipidemia, glucose intolerance, and the metabolic syndrome. So, management of HTN should be in a multidisciplinary approach focused not only in lowering blood pressure but should include a reduction in stress level, body weight control, dietary measures such as salt and carbohydrates restriction, and also avoiding saturated fat and promotion of daily exercise [1,13].

### Syndrome of hypertension: The role of risk factor clustering

Framingham Study data indicate that elevated blood pressure tends to cluster with other major risk factors such as stress, obesity, dyslipidemia, glucose intolerance, and left ventricular hypertrophy (LVH). Less than 20% of hypertension occurs in the absence of one or more of the following risk factors including high triglyceride (TG) and low density lipoprotein (LDL) cholesterol levels, reduced high density lipoprotein (HDL) cholesterol levels,

glucose intolerance, hyperinsulinemia, obesity, and LVH. The average number of risk factors also increased with the body mass index (BMI). Each of the risk factors found to cluster with hypertension was also found to predispose to its occurrence. Obesity, particularly abdominal adiposity, has been found to promote insulin resistance. Insulin resistance and compensatory hyperinsulinemia are related to hypertension in a graded fashion [14]. It has been estimated that about half of hypertensive persons have insulin resistance [15]. Obesity-induced insulin resistance is associated with lipoprotein lipase abnormality leading to increased triglyceride levels, reduced HDL cholesterol levels, and accumulation of very low-density LDL (vLDL). Hyperinsulinemia is also associated with glucose intolerance and hypertension which in turn also accelerate atherogenesis. Reaven and Chen [15] have postulated that hyperinsulinemia produced by insulin resistance stimulates the sympathetic nervous system (SNS) contributing to development of hypertension[16]. Among persons with an HTN in the Framingham Study, about 30% of coronary events in men and 70% in women were attributable to clusters of two or more additional risk factors [16].

The term of syndrome of hypertension, firstly described since 2004 during the annual meeting of world hypertension league, was attributed to clustering of risk factors in association with arterial hypertension in almost 92% of patients. These included obesity in 37%, smoking in 37.7%, type 2 diabetes mellitus (T2DM) and pre diabetes in 26%, dyslipidemia in 36% and family history of CAD in 46% [17]. In this study, myocardial perfusion imaging (MPI) single photon emission computed tomography (SPECT) imaging and echocardiography were performed for 214 high risk hypertensive patients (two or more cardiovascular risk factors for CAD) complaining of chest pain. Illustrated MPI of hypertensive patients presented at our chest pain unit with acute retrosternal chest pain, [A] SPECT perfusion study revealed large degree of tracer redistribution affecting the left anterior descending and right coronary artery territories and [B] MPI depicting apical, mid anterior and anterior septal reversible perfusion myocardial defects. Interestingly, the reversible myocardial perfusion defects (ischemic myocardial segments) were documented in 46 % of patients enrolled in our study. The sensitivity, specificity and diagnostic accuracy of treadmill exercise stress test were 77%, 38% and 56%, respectively in hypertensive patients with LVH when compared to MPI and coronary angiography [17].

The influence of hypertension on the full clinical spectrum of CVDs including sudden death, silent and overt myocardial infarction, heart failure and clinical and silent strokes is well established nowadays. Consequently, control of hypertension and its cardiovascular consequences required the correction of many clinical misconceptions about hypertensive vascular disease (HVD) such as the significance of left ventricular hypertrophy, proteinuria and the role of obesity, and weight gain [1,13,18].

### Preclinical detection of cardiovascular disease in hypertensive population

MPI is considered as the non-invasive technique of choice for quantitative assessment of CAD in a subset of high risk population presenting with chest pain and multiple risk factors for CAD. On the other hand, exercise stress treadmill test tends to lack the sensitivity, specificity and diagnostic accuracy among hypertensive patients who are presented with retrosternal chest pain.

### Echocardiography at rest and during stress

The accuracy of stress echocardiography (SE) for detection of significant coronary stenosis ranges from 80–90%, exceeding that of the exercise ECG (especially in women and patients with LVH and being comparable to that of SPECT. SE is a powerful prognostic tool in chronic CAD, after myocardial infarction and in evaluation of patients before major non-cardiac surgery [19, 20].

Furthermore, myocardial ischemia at dobutamine SE represents an independent predictor of risk of cardiac death even when angiographic anatomy is known, as prescribed by Marwick since 2002 [19,20]. illustrated time course graphs for the use of stress echocardiography to predict mortality in patients with diabetes and known or suspected CAD.

So, we learnt from Marwick study that functional significance of CAD is more

important and accurate in predicting the mortality, rather than the anatomical significance of the diseased coronary artery.

**Tissue Doppler (TDE) and strain by speckle tracking echocardiography (STE):** Detection of early subclinical myocardial disease is difficult when using resting conventional two dimensional echocardiographic (2DE) techniques that can evaluate either only the chamber systolic left ventricular ejection fraction (LVEF) or diastolic function. However, more specific parameters can be obtained by either TDI or STE methods, such as longitudinal, circumferential and radial myocardial velocities, strain and strain rate and if these investigations are used in combination with SE, myocardial abnormalities, as a response to the stress, can be identified with a higher degree of accuracy [21].

LVEF is load-dependent and therefore it is less sensitive than deformation imaging (strain and strain rate imaging) for accurate evaluation of global or regional myocardial function indices. For assessing the systolic function, peak systolic myocardial velocities are measured and the functional systolic reserve is calculated as the absolute or percentage increase of the velocities' values from baseline (resting) to peak stress. Similarly, for diastolic function peak early diastolic myocardial velocities are measured ( $e'$ ) and the diastolic functional reserve is calculated as the absolute or percentage increase of the velocities from baseline to peak stress. In the absence of cardiac disease,  $e'$  increases to a similar extent to the increase in trans mitral early (E) flow velocity so that, normally, the  $E/e'$  ratio (known as a good marker for estimating the LV filling pressures) remains unchanged at stress test. On the other hand, when diastolic dysfunction exists, the increased left atrial pressure determines an increase in mitral E flow velocity, while myocardial  $e'$  remains reduced, given the limited preload effect on it, and the  $E/e'$  ratio increases [22].

Strain (measuring the percentage of myocardial shortening or lengthening) and strain rate (the rate at which the myocardium changes its length) provide a more sensitive assessment of myocardial contraction and relaxation than displacement or tissue velocities. Recently introduced 2DE methods for assessment of strain and strain rate STE, eliminate the angle dependency of these Doppler-based techniques [23]. Accordingly, a better preventive and therapeutic strategies could be established by detecting a reduced global systolic strain (GLS) and functional reserve in this category of hypertensive patients at high risk of heart failure (HF) development, with important public-health implications [24].

Interestingly, there is growing evidence that the functional systolic and diastolic reserve is decreased even in the early, subclinical stages of cardiac dysfunction that exists in hypertensive disease and that the decrease seems to be related to the number of associated cardiovascular risk factors. These changes provide new targets for preclinical diagnosis and for monitoring responses to preventive strategies [24,25].

Recent advances in cardiac imaging techniques as STE, computed tomography and Cardiac Magnetic Resonance Imaging (CMR) can help in the preclinical detection of patients at risk of MCVE and SCD. According to the available worldwide data of increasing incidence of HF and SCD among hypertensive population who are presumably considered at low risk of cardiac death, certain emerging imaging modalities are crucial to identify such group of patients. Currently, STE is very helpful in identifying certain categories of patients presumably considered at low risk of MCVE. The clinical use of STE in cardiac assessment is widespread, with demonstrated benefit in various cardiac conditions, including assessment of coronary ischemia, assessment and prognostication of cardiomyopathies (ischemic and non-ischemic) and differentiation of hypertrophy. Two-dimensional GLS is a powerful predictor of cardiac mortality and morbidity in various cardiac conditions, with 2-D GLS and 2-D global circumferential strain (GCS) providing additional prognostic information over LVEF assessment alone [26]. Interestingly, GLS speckle tracking echocardiography could identify early abnormalities in left ventricle function in HTN in the presence of LVH and during family screening of different forms of hypertrophic cardiomyopathies. Furthermore, certain hypertensive and hypertrophic cardiomyopathy cases did not show either any ECG abnormalities or LVH by conventional 2-DE. However, they showed depressed GLS by STE [27-29]. how to obtain the bulls eye technique of automated function imaging which can be generated from apical 2,3 and 4 chamber views

which illustrated an impaired GLS of -13% in hypertensive patient, although LVEF was still in the normal range (51%), (A) Showed 2DE an apical 4 chamber view in the presence of moderate mitral incompetence, (B) Depressed GLS (-13%), (C) showed normal LVEF by 2-DE and (D) Showed depressed maximal rate of pressure rise during ventricular contraction (Peak  $dp/dt = 645$  mmHg/s), with positive correlation to GLS but not with LVEF.

The early clinical abnormalities in global longitudinal peak systolic strain STE (systolic dysfunction) and diminished E annular velocity (diastolic dysfunction) by TDE can be demonstrated in apparently a symptomatic hypertensive patients [26-29]. Diabetes and hypertension, which are often associated with the impairment of longitudinal function, are also common findings in patients with heart failure with preserved ejection fraction (HFpEF) and it is well known that LVH is the key structural change of this disease. Probably, repetitive ischemic insults due to macro vascular and micro vascular abnormalities and interstitial fibrosis cause an early intrinsic depression of subendocardial longitudinal fiber contractility in these patients, especially in more hypertrophic hearts. For this reason, longitudinal myocardial performance is early impaired, whereas in the first stage of the disease the sparing of circumferential fibers results in LVEF remaining within the normal range [29]. So, GLS provides additional information in the evaluation of LVH, and regional changes in longitudinal strain seem to identify specific myocardial deformation patterns for some forms of myocardial hypertrophy. It is clear nowadays that myocardial fiber mechanical dysfunction precedes histopathological changes such as fibrosis and hypertrophy in essential hypertension which can be detected in the preclinical stage of the disease, through a reduced tissue Doppler – derived systolic and diastolic velocities and depressed GLS either before or even without the development of LVH, [26-29]. Similarly, Helling Wen et al., demonstrated the feasibility of detecting early left ventricular systolic dysfunction using global area strain derived from three-dimensional STE [30]. These investigators found a high sensitivity of area strain (integrating longitudinal and circumferential deformation) in detecting early and subtle left ventricular (LV) dysfunction in patients with risk factors of HF [30].

Furthermore, Thor Edvardsen and his colleagues revealed an early systolic dysfunction criteria of the LV evidenced by STE in heart failure with normal ejection fraction (HFpEF) [31].

Generally, global longitudinal systolic strain STE and TDI are of crucial importance in the preclinical diagnosis of myocardial diseases specifically in hypertensive heart disease, hypertrophic cardiomyopathy (HCM) and diabetes- induced cardiomyopathy. Recently, STE is used as an important tool in the diagnosis of acute coronary syndromes (ACS) in critical care departments, which can add greatly to the triage of diagnosis of ACS although, the technology is not sufficiently standardized to be recommended as a general tool for this purpose [32].

In summary, myocardial strain is an important clinical tool for the quantification of left ventricular (LV) function which is now feasible with STE. The best evaluated strain parameter is global longitudinal strain (GLS) which is more sensitive than LVEF as a measure of systolic function, and can be used to identify sub-clinical LV dysfunction in different cardiovascular diseases.

### **Value of Cardiac Magnetic Resonance imaging (CRM) in the assessment of hypertensive heart disease (HHD)**

Hypertensive heart disease is characterized by LVH, left atrial dilatation, myocardial fibrosis, diastolic prior to systolic dysfunction, and increased incidence of CAD. Hypertensive vascular disease manifests as aortic wall pathology such as increased prevalence of atheromatous plaques and higher risk of aneurysm, dissection, penetrating ulcer, intramural hematoma or PAD [33]. CRM can identify the pathophysiology of hypertension disease process and provides accurate and reproducible measures of ventricular volumes, mass, function, geometry of LV and hemodynamics as well as uniquely allowing tissue characterization of diffuse and focal fibrosis [34]. CRM can detect as well an increased type I pro collagen synthesis by late gadolinium myocardial enhancement (LGE). CRM has been proposed as preclinical marker of those patients with cardiac hypertrophy at risk of ventricular arrhythmias and SCD [34]. Furthermore, LGE has been used to identify areas of myocardial fibrosis,

which is arrhythmogenic in cardiomyopathy and some cases of mitral valve prolapsed syndrome as well [35]. Advances in CMR have made it possible to evaluate both the structure and function of the heart. Extensive LGE by CMR can identify high-risk patients with LVH and HCM as well. This is an independent predictor of SCD, a quantitative assessment of myocardial fibrosis by LGE and as such, it can thus be a clinically useful tool in order to help risk stratify patients with cardiac hypertrophy whether he/she has inherited disease as HCM, idiopathic LVH or in association with HHD [33-35]. Furthermore, a meta-analysis by Green et al. [35] showed significant associations between the presence of LGE and cardiovascular mortality, HF death, and all-cause mortality .

## Imaging of atherosclerosis: Who are at risk of acute coronary syndromes (ACS) and SCD?

### Pathophysiology

Atherosclerosis is the primary cause of heart disease and stroke. In Westernized societies, it is the underlying cause of about 50% of all deaths. Epidemiological studies have revealed several important environmental and genetic risk factors associated with atherosclerosis. Over the past decade, the availability of new investigative tools has resulted in a clearer understanding of the molecular mechanisms that connect altered cholesterol metabolism and other risk factors in the development of atherosclerotic plaque. It is now clear that atherosclerosis is a chronic inflammatory condition that can be converted into an acute clinical event by plaque rupture and thrombosis [36, 37].

Multimodality approach to atherosclerosis imaging is in great progress to identify vulnerable atherosclerotic plaque liable to rupture. This is the leading cause of death in 50% or more of patients who died suddenly. Each modality offers unique measurements of disease severity. Together, this information can be used to determine anatomic and hemodynamic consequences of atherosclerosis, complimented by detail on plaque composition, overall disease burden, and current metabolic activity acting within an individual patient [38].

Computed tomographic (CT) angiography can show the component of the plaque (non- calcified or calcified) in the relevant coronary artery with positive remodelling. It can also assess as well calcium scoring, atherosclerotic plaque vulnerability and predict patients who are at high risk of developing plaque rupture and ACS [38].

Moreover, optical coherence tomography (OCT) image of a coronary plaque can display lipid rich lesion liable to rupture, characterized as signal-poor regions with poorly demarcated borders. A lipid-rich coronary plaque, displaying thin overlying fibrous cap indicative of thin-cap fibro atheroma, is an important sign of vulnerable plaque [38]. In addition, Fused <sup>18</sup>F-NaF positron emission tomography (PET)-CT image is able to show high coronary artery tracer uptake revealing an active plaque micro calcification [38].

Although risk stratification and a great progress in multimodality imaging are useful to identify hypertensive individuals at risk for MCVE (ACS, HF and SCD), current techniques to identify high-risk individuals lack sufficient predictive value to have clinical utility because of the relatively low event rates or absolute risk. Accordingly, carotid artery ultrasound, which measures carotid intima media thickness (cIMT) can detect early atherosclerosis and advanced atheromatous plaques. This is a strong indicator of overall vascular health. cIMT is well recognized and also an accepted marker to predict cardiovascular disease and stroke in particular [39].

In comparison to CT scan which carries radiations hazards of stochastic effect, carotid ultrasounds and myocardial contrast echocardiography (MCE) are safe and promising non-invasive tools for risk stratification of CAD in high risk population.

## Conclusion

An important disclosure in epidemiologic hypertension research revealed that hypertension is a syndrome usually presenting in conjunction with other metabolically linked risk factors. As such, control of hypertension and

its cardiovascular consequences required the correction of many clinical misconceptions about HHD such as the significance of LVH, proteinuria, dyslipidemia and the role of obesity, and insulin resistance syndrome. Preclinical detection of myocardial dysfunction in HTN could be detected by STE and other emerging imaging modalities with high accuracy. These changes provide new targets for preclinical diagnosis and for monitoring responses to preventive strategies. Moreover, a better preventive and therapeutic strategy could be established by detecting a reduced GLS and functional reserve in this category of hypertensive patients at high risk of heart failure development, with important public-health implications. Finally, a multidisciplinary approach is crucial for assessment of early atherosclerosis and assessment of major risk factors associated with arterial hypertension for proper selection of treatment strategy.

## References

1. Paul Whelton, Robert M, Wilbert S, Donald E. and Karen J. et al. "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines" . *Hypertension*(2018) 6: 13–115
2. Kearney PM, Whelton M, Reynolds K, Muntner P and Whelton PK et al. "Global burden of hypertension: analysis of worldwide data". *The lancet*. (2005) 365(9455):217-223.
3. Forouzanfar MH, Alexander L and Anderson HR.GBD. "Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study." *Lancet* (2015) 386 (10010):2287-323.
4. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M and Das SR et al. "Heart disease and stroke statistics—2017 update: a report from the American Heart Association". *Circulation* (2017) 135(10):e146-603.
5. Stamler J, Neaton JD, Cohen JD, Cutler J and Eberly L et al. "Multiple risk factor intervention trial revisited: A new perspective based on nonfatal and fatal composite endpoints, coronary and cardiovascular, during the trial". *J Am Heart Assoc*. (2012) 1(5):e003640.
6. Yano Y, Reis JP, Colangelo LA, Shimbo D and Viera AJ et al. "Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guidelines with Cardiovascular Events Later in Life". *JAMA* (2018) 320(17):1774-1782.
7. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M and Das SR et al. "Heart Disease and Stroke Statistics—2017 Update :A Report From the American Heart Association". *Circulation* (2017) 135(10): e146–603.
8. Kannel, WB. "Risk stratification in hypertension: New insights from the Framingham study". *Am J Hypertens*(2000) 13:3S–10S.
9. Lewington S, Clarke R and Qizilbash N. "Age-specific relevance of usual blood pressure to vascular mortality : a meta analysis of individual data for one million adults in 61 prospective studies". *Lancet* (2002) 360: 1903-1913.
10. Son JS, Choi S, Kim K, Kim SM and Choi Det al. "Association of blood pressure classification in Korean young adults according to the 2017 American college of cardiology/American Heart Association guidelines with subsequent cardiovascular disease events". *JAMA*(2018) 320 (17):1783-1792.
11. Verdecchia P, Angeli F, Reboldi G. "Hypertension and atrial fibrillation: Doubts and certainties from basic and clinical studies". *Circulation Research* (2018) 122:352–368.

12. Shen L, Ma H, Xiang MX and Wang JA. "Meta-analysis of cohort studies of baseline prehypertension and risk of coronary heart disease". *AM J Cardiol.* (2013) 112(2):266-271.
13. Ninomiya T and Perkovic V. "Blood pressure lowering treatment trialists collaboration: Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: Meta-analysis of randomized controlled trials". *BMJ* 347: f5680.
14. Zaveroni I, Bonora E, Pagliara M, Dall'Aglio E and Luchetti L et al. "Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance". *N Engl J Med*(1989) 320:702–706.
15. Reaven GM, Chen YI. "Insulin resistance, its consequences, and coronary heart disease: must we choose one culprit?". *Circulation*(1996) 93(10):1780-1783.
16. Kannel WB. "Framingham study insights into hypertensive risk of cardiovascular disease". *Hypertens Res.* (1995) 18(3):181–196.
17. Elkilany GE, Al-Qbandi MA, Sayed KA and Kabbash I. "Dilated cardiomyopathy in children and adults: what is new?". *The Scientific World JOURNAL* (2008) 8:762-775.
18. Kannel WB. "Hypertension: Reflections on risks and prognostication". *Med Clin North Am* (2009) 93(3):541-558.
19. Marwick TH, Case C, Sawada S, Vasey C and Short L et al. "Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease". *Diabetes Care* (2002) 25(6):1042-1048.
20. Thomas H Marwick "Stress cardioagraphy". *Heart* (2003) 89:113–118.
21. Francis GS and Desai MYJ. Contractile reserve: Are we beginning to understand It?". *AmCollCardiolmng* (2008) 1:727–728.
22. Oh JK, Park SJ and Nagueh S. "Established and novel clinical applications of diastolic function assessment by echocardiography". *Circ Cardiovasc Imaging.* (2011) 4(4):444-455.
23. Dandel M, Lehmkühl H, Knosalla C, Suramelashvili N and Hetzer R. "Strain and strain rate imaging by echocardiography – Basic concepts and clinical applicability". *Current Cardio Rev*(2009) 5(2) 133-148.
24. Patrascu N. "Assessment of Systolic and Diastolic Cardiac Function beyond Traditional Markers in Hypertensive Patients. Role of Cardiac Reserve". *Maedica* (2013) 8(2):214.
25. Vinereanu D, Mädler CF, Gherghinescu C, Ciobanu AO and Fraser AG. "Cumulative impact of cardiovascular risk factors on regional left ventricular function and reserve: Progressive long-axis dysfunction with compensatory radial changes". *Echocardiography* (2011) 28(8):813-820.
26. Luis SA, Chan J and Pellikka PA. "Echocardiographic assessment of left ventricular systolic function: An overview of contemporary techniques, including speckle-tracking echocardiography". *Mayo ClinProc* (2019) 94(1): 125-138.
27. Elkilany GN, Allah SB, Fedacko J, Singh J and Singh RB et al. "Hypertensive cardiomyopathy: Diagnostic approach and clinical differentiation from hypertrophic cardiomyopathy". *J Cardiol & Cardiovasc Ther* (2019) 15(4): 001-008.
28. Elkilany GE and Kabbash I. "How to identify latent systolic dysfunction and post operative risk in patients with mitral incompetence and normal ejection fraction?". *World J Cardiovasc Surg* (2011) 1: 11-17.
29. Todaro MC, Khandheria BK, Longobardo L, Zito C and Cusmà-Piccione M et al. "New diagnostic perspectives on heart failure with preserved ejection fraction: Systolic function beyond ejection fraction". *J of Cardiovasc Med* (2015) 16(8):527-537.
30. Wen H, Liang Z, Zhao Y and Yang K. "Feasibility of detecting early left ventricular systolic dysfunction using global area strain: A novel index derived from three-dimensional speckle-tracking echocardiography". *Euro J Echocardiogr* (2011) 12(12):910-916.
31. Edvardsen T, Helle-Valle T and Smiseth OA. "Systolic dysfunction in heart failure with normal ejection fraction: Speckle-tracking echocardiography". *Prog Cardiovasc Dis* (2006) 49(3):207-214.
32. Kukulski T, Jamal F, Herbots L, D'hooge J and Bijmens B et al. "Identification of acutely ischemic myocardium using ultrasonic strain measurements: A clinical study in patients undergoing coronary angioplasty". *J Am Coll Cardiol* (2003) 41(5):810-819.
33. Maceira AM, Mohiaddin RH. "Cardiovascular magnetic resonance in systemic hypertension". *Journal of Cardiovascular Magnetic Resonance* (2012) 14(1): 1-7.
34. Weng Z, Yao J, Chan RH, He J and Yang X et al. "Prognostic value of LGE-CMR in HCM: a meta-analysis". *JACC: Cardiovascular Imaging* (2016) 9(12):1392-1402.
35. Green JJ, Berger JS, Kramer CM and Salerno M. "Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy". *JACC: Cardiovascular Imaging* (2012) 5(4):370-377.
36. Ross R. "The pathogenesis of atherosclerosis: A perspective for the 1990s". *Nature* (1993) 362(6423):801-809.
37. Marques JS, Pinto FJ. "The vulnerable plaque: Current concepts and future perspectives on coronary morphology, composition and wall stress imaging". *Rev Port Cardiol* (2014) 33(2):101-110.
38. Tarkin JM, Dweck MR, Evans NR, Takx RA and Brown AJ et al. "Imaging atherosclerosis". *Circ Res* (2016) 118(4):750-769.
39. Stein JH, Korcarz CE, Hurst RT, Lonn E and Kendall CB, et al. "Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: A consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force endorsed by the Society for Vascular Medicine". *J Am Soc Echocardiogr* (2008) 21(2):93-111.
40. Whelton PK, Carey RM, Aronow WS, Casey DE and Collins KJ et al. "ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines". *J Am Coll Cardiol* (2018) 71:127-248.
41. GBD 2015 Risk Factors Collaborators. "Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015." *Lancet* (2016) 388:1659.

**How to cite this article:** Luigi P. Badano, NS Dhalla, Yomna Galal Elkilany, Sherif Baath Allah, Jaipaul Singh, Ram B Singh, et al. "Pre-clinical Detection of Cardiac Dysfunction and Coronary Artery Disease in Essential Hypertension: An Update." *J Hypertens (Los Angel)* 10 (2021): 278.