Conflicts of interest

None declared.

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References

[1] Li DG, Di Xia F, Khosravi H, et al. Outcomes of early dermatology consultation for inpatients diagnosed with cellulitis. JAMA Dermatol February 2018. https://doi.org/10.1001/jamadermatol.2017.6197.
[2] Weng QY, Raff AB, Cohen JM, et al. Costs and consequences associated with misdiagnosed lower extremity cellulitis. JAMA Dermatol 2017;153(2):141–6. https://doi.org/10.1001/jamadermatol.2016.3816.
[3] Overview of the Nationwide Emergency Department Sample (NEDS). https://www.hcup-us.ahrq.gov/nedsoverview.jsp. [Accessed March 7, 2018].
[4] Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol 2007;60(4):397–409. https://doi.org/10.1016/j.jclinepi.2006.07.011.
[5] Singh JA, Yu S. Utilization due to chronic obstructive pulmonary disease and its predictors: a study using the U.S. National Emergency Department Sample (NEDS). Respir Res 2016;17(1). https://doi.org/10.1186/s12931-015-0319-y.
[6] Raff AB, Weng QY, Cohen JM, et al. A predictive model for diagnosis of lower extremity cellulitis: a cross-sectional study. J Am Acad Dermatol 2017;76(4):618–625.e2. https://doi.org/10.1016/j.jaad.2016.12.044.

Heart rate variability in the risk stratification of emergency department patients with chest pain

Chest pain is the second most common presenting complaint in the emergency department (ED), accounting for 8–10 million ED visits per year and between $10–13 billion dollars per year in ED costs [1, 2]. Several scoring systems developed recently have attempted to stratify patients based on their risk for major adverse cardiac events. The HEART score is a prospectively studied scoring system designed to identify patients who are at highest risk of a major adverse cardiac event (MACE) in the next 6 weeks [3-5], and this score is used as a part of chest pain management protocols in many hospitals.

Heart rate variability (HRV) is a physiologic parameter that is altered in many conditions including heart disease, hypertension, hyperlipidemia, obesity, smoking and diabetes and is associated with increased mortality in patients following myocardial infarction [6-15]. Based on these findings, HRV presents a promising strategy to differentiate chest pain patients who will be diagnosed with ACS. We conducted a prospective observational study of patients presenting to a 65,000-visit academic Midwestern ED with a chief complaint of chest pain. The objective of our study was to measure the diagnostic utility of HRV in diagnosing ACS among ED patients with chest pain. Using a 10-min heart tracing performed in the ED, we assessed the correlation between HRV with 30-day MACE, HEART score, and cardiovascular risk factors. Inclusion criteria included age > 30, no obvious traumatic or non-cardiac cause of chest pain, and sinus rhythm. Those with ST-elevation myocardial infarction (STEMI) were excluded from the study.

Our hypothesis was that lower HRV in the ED is associated with ACS measured by 30-day MACE, higher HEART score, and more cardiovascular (CV) risk factors. Our primary endpoint was MACE diagnosed during index hospitalization or within 30 days of ED visit. Secondary endpoints included associations between HRV and HEART score and CV risk factors. HRV is measured and analyzed in many ways, we used frequency domain measures including low frequency (LF), high frequency (HF), LF/HF ratio, and total power (TP).

Sixty patients were included in the final analysis. Our sample population was 58% percent women with mean age of 55 (Table 1). 92% of participants had at least one cardiovascular risk factor. Admission rate was 65%. Six participants experienced the primary endpoint of MACE: three patients were diagnosed with non-ST-elevation myocardial infarction and one patient underwent PCI for unstable angina during the index hospitalization. Two additional patients experienced MACE in the subsequent 30 days. One patient died due to unknown causes, and 1 additional patient underwent PCI for a critical coronary stenosis found on coronary angiogram. There were no significant associations found between HRV and the primary outcome MACE (all $p > 0.05$), Table 2.

Table 3 shows the results of univariate regression analysis of the association between HEART score and HRV. Table 4 shows the results of univariate regression analysis between the five HEART score parameters and HRV. Notably, significant associations were found between HEART score and heart rate variability. Lower HRV was associated with higher heart score. Within the Risk Factors category (Table 5), diabetes and hypertension appeared to drive the association between increased risk factors and less heart rate viability.

In this observational prospective study measuring HRV in patients presenting to the ED with chest pain, we found a significant

Table 1
Patient characteristics.

Parameter	N (%)
Women	35 (58)
Prior MACE	23 (38)
HTN	36 (60)
HLD	34 (57)
DM	17 (28)
Smoking	23 (38)
Obesity	27 (45)
Family history	33 (55)
Age, mean (range)	55 (30–87)

Patient characteristics with respect to cardiovascular risk factors.

Table 2
Association between primary outcome, MACE[a], and heart rate variability

HRV parameter	MACE Odds ratio, 95% confidence interval	*P*-value
TP	1.00 (0.99–1.00)	0.20
LF/HF	1.22 (0.82–1.81)	0.33
LF	1.00 (0.99–1.00)	0.09
HF	0.99 (0.99–1.00)	0.94

Results of univariate logistic regression to evaluate associations between four HRV parameters and MACE.
[a] Includes combined MACE during index hospitalization and within 30 days of presentation.

Table 3
Association between secondary outcome, HEART score, and heart rate variability.

HRV parameter	Beta (95% confidence interval)	*P*-value
TP	−0.000 (−0.001, −0.000)	0.009
LF/HF	−0.033 (−0.283, 0.216)	0.791
LF	−0.000 (−0.001, 0.000)	0.200
HF	−0.001 (−0.002, −0.000)	0.004

Results of univariate linear regression to evaluate associations between four HRV parameters and HEART score.

Table 4
Association between HEART score categories and heart rate variability.

		Beta (95% confidence interval)	*P*-value
HPI	TP	−880.563 (−1740.415, −20.711)	0.045
	LF/HF	−0.457 (−1.283, 0.370)	0.273
	LF	−200.689 (−539.650, 138.271)	0.241
	HF	−257.250 (−471.392, −43.108)	0.019
ECG	TP	−788.195 (−1805.43, 229.04)	0.126
	LF/HF	0.283 (−0.688, 1.254)	0.562
	LF	−60.757 (−460.364, 338.849)	0.762
	HF	−163.737 (−421.978, 94.503)	0.209
Troponin	TP	440.473 (−738.688, 1619.636)	0.458
	LF/HF	0.127 (−0.983, 1.238)	0.819
	LF	28.201 (−428.184, 484.588)	0.902
	HF	−66.228 (−364.523, 232.066)	0.658
Age	TP	−40.651 (−80.146, −1.157)	0.044
	LF/HF	−0.018 (−0.056, 0.020)	0.341
	LF	−9.268 (−24.841, 6.304)	0.238
	HF	−6.943 (−17.099, 3.212)	0.176
Risk factors	TP	−1041.606 (−1797.976, −285.237)	0.008
	LF/HF	0.195 (−0.556, 0.949)	0.604
	LF	−163.052 (−469.959, 143.855)	0.292
	HF	−266.469 (−456.854, −76.084)	0.007

Results of univariate linear regression to evaluate associations between four HRV parameters and the five defined HEART score categories.

association between HRV and HEART score, but no association between HRV and MACE. This association seems to be driven by correlation between HRV and cardiovascular risk factors, particularly diabetes and hypertension.

Table 5
Association between cardiovascular risk factors and heart rate variability.

		Beta (95% confidence interval)	*P*-value
DM	TP	−1247.335 (−2345.553, −149.117)	0.027
	LF/HF	−0.455 (−1.523, 0.613)	0.397
	LF	−530.759 (−949.670, −111.848)	0.014
	HF	−156.675 (−442.764, 129.412)	0.278
HLD	TP	−686.362 (−1712.848, 340.124)	0.186
	LF/HF	−0.462 (−1.433, 0.507)	0.344
	LF	−99.083 (−499.744, 301.576)	0.622
	HF	−207.737 (−464.840, 49.365)	0.111
HTN	TP	−1406.5 (−2393.768, −419.232)	0.006
	LF/HF	0.094 (−0.894, 1.083)	0.849
	LF	−318.888 (−716.272, 78.494)	0.114
	HF	−265.069 (−521.639, −8.500)	0.043
Family history	TP	−324.127 (−1358.742, 710.486)	0.533
	LF/HF	0.007 (−0.966, 0.980)	0.988
	LF	95.639 (−303.495, 494.774)	0.633
	HF	−44.545 (−306.085, 216.994)	0.734
Obesity	TP	−715.400 (−1736.345, 305.544)	0.166
	LF/HF	0.345 (−0.624, 1.315)	0.478
	LF	−155.909 (−553.729, 241.911)	0.436
	HF	−225.488 (−480.493, 29.517)	0.082
Smoking	TP	−450.3, (−1505.960, 605.280)	0.397
	LF/HF	0.392, (−0.599, 1.383)	0.432
	LF	68.82, (−399.997, 477.635)	0.737
	HF	−141.21, (−406.51, 124.09)	0.291

Results of univariate linear regression to evaluate associations between four HRV parameters and the six cardiovascular risk factors.

This is consistent with prior research that has demonstrated altered levels of HRV in coronary artery disease, diabetes, hypertension, hyperlipidemia, obesity, and smoking [10-21].

An important recent study on this topic published in AJEM in 2013 attempted to incorporate HRV parameters into a novel risk score for MACE [22]. In their study, 25 of 309 total participants reached the primary composite outcome of serious cardiac events within 72 h of ED presentation. They found that a lower LF/HF ratio to be most associated with their primary endpoint, but no information on association with cardiac risk factors was published. They concluded that HRV measurement has the potential to be a predictive tool for risk stratification of ED patients with chest pain. While this finding may be true, our data suggests that much of the predictive value may be through the causal pathway of cardiac risk factors, rather than an independent factor that can identify early coronary ischemia.

Our study is limited by a small number of participants sustaining the primary endpoint (MACE) which makes that portion of the analysis irrelevant.

HRV is associated with HEART score in patients presenting to an ED with chest pain, but this association is almost entirely mediated by comorbid cardiac risk factors. Further work on this topic may focus on how HRV parameters can be used in the context of risk factor assessment in clinical decision rules.

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References

[1] Owens PL, Barrett ML, Gibson TB, Andrews RM, Weinick RM, Mutter RL. Emergency department care in the United States: a profile of national data sources. Ann Emerg Med 2010:1097–6760 (Electronic).
[2] Simon A. Chest pain. In: Tintinalli JESJ, Ma O, Yealy DM, Meckler GD, Cline DM, editors. Tintinalli's emergency medicine: a comprehensive study guide. 8th Edition. New York, NY: McGraw-Hill; 2016.
[3] Backus BE, Six AJ, Kelder JC, Bosschaert MAR, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 2013;168(3):2153–8.
[4] Mahler SA, Riley RF, Hiestand BC, et al. The HEART pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. Circ Cardiovasc Qual Outcomes 2015:1941–7705 (Electronic).
[5] Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Int J Cardiol 2013:1568–5888 (Print).
[6] Casolo GC, Stroder P, Signorini C, Calzolari F, et al. Heart rate variability during the acute phase of myocardial infarction. Circulation 1992:0009–7322 (Print).
[7] Huikuri HV, Seppanen T, Koistinen MJ, Airaksinen J, et al. Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. Circulation 1996: 0009–7322 (Print).
[8] Kleiger RE, Miller JP, Bigger Jr JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987:0002–9149 (Print).

[9] Laitio TT, Makikallio TH, Huikuri HV, Kentala ESH, et al. Relation of heart rate dynamics to the occurrence of myocardial ischemia after coronary artery bypass grafting. Am J Cardiol 2002:0002–9149 (Print).
[10] Gottsater A, Ahlgren Ar, Taimour S, Sundkvist G. Decreased heart rate variability may predict the progression of carotid atherosclerosis in type 2 diabetes. Clin Auton Res 2006:0959–9851 (Print).
[11] Harte CB, Meston CM. Effects of smoking cessation on heart rate variability among long-term male smokers. Int J Behav Med 2014:1532–7558 (Electronic).
[12] Karason K, Molgaard H, Wikstrand J, Sjostrom L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999:0002–9149 (Print).
[13] Liao D, Sloan RP, Cascio WE, Folsom AR, et al. Multiple metabolic syndrome is associated with lower heart rate variability. The Atherosclerosis Risk in Communities study. Diabetes Care 1998:0149–5992 (Print).
[14] Schroeder EB, Liao D, Chambless LE, Prineas RJ, Prineas RJ, Evans Gw, Heiss G. Hypertension, blood pressure, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Hypertension 2003:1524–4563 (Electronic).
[15] Harris PR, Stein PK, Fung GL, Drew BJ. Heart rate variability measured early in patients with evolving acute coronary syndrome and 1-year outcomes of rehospitalization and mortality. Vasc Health Risk Manag 2014:1178–2048 (Electronic).
[16] Dekker JM, Crow RS, Folsom AR, Hannan PJ, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis risk in communities. Circulation 2000: 1524–4539 (Electronic).
[17] Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. The BMJ 2015;351:h5527. https://doi.org/10.1136/bmj.h5527.
[18] Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-Aho PO, Karjalainen PA. Kubios HRV–heart rate variability analysis software. Comput Methods Prog Biomed 2014: 1872–7565 (Electronic).
[19] Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes: the atherosclerosis risk in communities (ARIC) study. Diabetes 2002: 0012–1797 (Print).
[20] Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: an intuition toward cardiac autonomic alteration - a risk of CVD. Diabetes Metab Syndr Obes 2017:1178–7007 (Linking).
[21] Doncheva NI, Nikolova Ri, Danev SG. Overweight, dyslipoproteinemia, and heart rate variability measures. Folia Med 2003:0204–8043 (Plovdiv). (Print).
[22] Ong ME, Goh K, Fook-Chong S, Haaland B, et al. Heart rate variability risk score for prediction of acute cardiac complications in ED patients with chest pain. Am J Emerg Med 2013:1532–8171 (Electronic).

Aortic dissection and aneurysm are hypertensive target organ damages and should be listed in the guidelines

To the Editor:

The significance of aortic (Ao) diseases derives from the prevalence, a dramatic clinical picture and a very high mortality rate in acute forms. Moreover, misdiagnosis and the economic burden are also not to be neglected.

The *prevalence* of abdominal aortic *aneurysm (AAA)* in men over 60 years old is about 5% and it doubles in men over the age of 80 years [1,2]. Aneurysms of thoracic aorta represent a 1/5 to a 1/4 of all Ao aneurysms [3]. In the US, AAA has been reported to be in the 13th place among the most important causes of death and in 3rd place in men who are older than 60 years as far as sudden death is concerned [1]. AAA (particularly a large one) is prone to rupture and if this occurs, every third patient will die before reaching the hospital. Moreover, the total *mortality* rate approaches 60–80% [4,5].

Aortic dissection (*AoD) incidence* is relatively low: 3–6 patients per 100,000 individuals annually [5,6], but the clinical picture is dramatic and the prognosis is grave. *Mortality* of *AoD* has been "exceedingly high" [7] and AoD has been among the deadliest diseases in emergency departments (ED) [6]. A significant number of AoD patients die prior to being admitted into hospital [8]. More than 1/4 of patients can die while in hospital even though they received appropriate treatment [6]. Moreover, Oxford Vascular Study reported that only 52.6% of patients with AoD who were hospitalized had managed to survive 30 days [8]. Therefore, it is very important to prevent such dangerous diseases.

Systemic arterial hypertension (HTN) has been a very important risk factor for Ao diseases. An overall prevalence of 0.3% has been identified during the screening for *AAA* in Japan in 1591 individuals and no less than 7.7% in patients with HTN [9]. In addition to smoking, male gender and advanced age, HTN is one of the crucial factors for AAA etiopathogenesis. Additionally, HTN increases the risk of rupture by 30% for each 10 mm Hg mean BP elevation [10]. Consequently, HTN is a well-known risk factor for AAA formation, enlargement and rupture [10,11]. During the screening of >3,000,000 people for AAA risk factors, insufficiently controlled BP had been measured in more than half of the patients with diagnosed HTN [12].

The most prevalent risk factor for *AoD* is HTN, which has been repeatedly found in 2/3 to 3/4 of patients [5,7]. In the majority of such AoD patients, BP has been insufficiently controlled [7]. Therefore, aneurysm and dissection of Ao represent very important target organ damages (TOD) of HTN.

Accordingly, *aorta should be listed among target organs* in the relevant guidelines (having in mind their importance). To our surprise, this has not been the case. Although the current guidelines for *HTN* are very good and despite the obvious significance of Ao diseases (such as Ao aneurysm and AoD), as well as the evidence-based importance of HTN in their genesis, Ao complications of HTN have not been listed in contemporary HTN guidelines properly [13-17]. For example, the Joint National Committee (JNC-8) guidelines focused on HTN treatment and in the JNC-7 AoD was not mentioned as TOD of HTN [15,18,19]. There is no obvious explanation to cite the *peripheral* arterial disease as TOD and to omit the *central* arterial (aortic) disease (e.g., Table 6 in JNC-7) [15].

In the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) 2013 HTN guidelines, the peripheral arteries are also listed in signs of TOD but Ao is not. In another place the authors recommend the ultrasound examination of the ascending Ao. Moreover, concerning HTN complications, there is a suggestion to search for Ao stiffness but not directly for Ao dilatation, aneurysm and (clinically unrecognized) dissection. For example, in Table 8.4 "History and symptoms of organ damage and cardiovascular disease", Ao consequences of HTN were not mentioned. Moreover, in Table 9, under the subheading: "Signs of organ damage", "Peripheral arteries" are mentioned but "Central arteries" (or „aorta") are not. In 2018 Canadian guidelines for HTN, in the Examples of TOD (4th Supplemental Table) the authors listed „Peripheral artery disease" but Ao diseases were not mentioned [16]. In the pragmatic National Institute for Health and Care Excellence (NICE) 2011 HTN guidelines Ao complications were also not cited among TOD [17].

As prevention is better than cure, the HTN - AoD relationship, most probably a causal one, ought to be mentioned in the HTN guidelines. Regarding the diseases with a causal relationship such as HTN (usually the cause) and AoD (consequence), it is important to write about this in the guidelines for both diseases. It is even more important to write about it in the guidelines for HTN (cause), in order that we may become more aware that a preventive effort is required. Hopefully the new 2018 ESC ESH hypertension guidelines will correct these shortcomings.

The only guidelines that have specifically addressed Ao diseases are the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guidelines [19]. There has been half a page dedicated to drug treatment of patients who have the Ao disease in addition to HTN. The authors correctly stated that studies of such patients had been missing and that target BP and the optimal antihypertensive medications have been unknown. They have recommended beta blockers [19]. Nevertheless, a lot of information about the aortic consequences of HTN, including the significance of HTN for Ao aneurysm and AoD, classification of Ao aneurysms and AoD as hypertensive TOD, recommendation when and how to screen for Ao aneurysms, as well as (scarce) information about the HTN characteristics that are risk markers for hypertensive Ao complications are missing.

Conclusion: As opposed to peripheral arterial disease, acute and chronic aortic complications of HTN have not been adequately listed in all the hypertension guidelines among the useful information in medical history, symptoms, hypertensive target organ damages and suggestions about which hypertensive lesion to look for. Having in mind the significance of the guidelines for the management of such an important