TABLE II
SCALING AND MULTIFRACTAL EXPONENTS c_1, c_2, c_3, c_4 ESTIMATED OVER SCALES [2.6, 81.9] S-MEDIAN (MED) AND MEDIAN ABSOLUTE DEVIATION (MAD)-P-VALUES FROM MANN-WHITNEY TEST

RR	NS: med	(mad)	SV: med	(mad)	p-value
c_1	0.104	(0.164)	0.156	(0.171)	0.07
c_2	−0.007	(0.049)	0.004	(0.054)	0.60
c_3	0.007	(0.040)	0.003	(0.037)	0.68
c_4	−0.045	(0.275)	−0.030	(0.298)	0.33
μ_{RR}	NS: med	(mad)	SV: med	(mad)	p-value
c_1	0.147	(0.155)	0.200	(0.175)	0.11
c_2	−0.027	(0.044)	−0.019	(0.060)	0.74
c_3	−0.019	(0.050)	−0.007	(0.048)	0.76
c_4	−0.068	(0.096)	−0.030	(0.064)	0.04
ξ_0	NS: med	(mad)	SV: med	(mad)	p-value
c_1	0.766	(0.062)	0.744	(0.095)	0.35
c_2	−0.192	(0.094)	−0.133	(0.118)	0.05
c_3	0.124	(0.254)	0.071	(0.207)	0.19
c_4	−0.340	(0.773)	−0.228	(0.423)	0.24
σ^2_{RR}	NS: med	(mad)	SV: med	(mad)	p-value
c_1	0.773	(0.058)	0.732	(0.093)	0.36
c_2	0.026	(0.120)	−0.009	(0.098)	0.23
c_3	0.016	(0.149)	0.033	(0.125)	0.91
c_4	−0.109	(0.489)	0.015	(0.538)	0.33
σ^2_{HR}	NS: med	(mad)	SV: med	(mad)	p-value
c_1	0.759	(0.066)	0.715	(0.096)	0.49
c_2	0.016	(0.118)	−0.008	(0.116)	0.24
c_3	−0.017	(0.186)	0.025	(0.164)	0.71
c_4	−0.155	(0.876)	−0.008	(0.705)	0.23
HF	NS: med	(mad)	SV: med	(mad)	p-value
c_1	0.549	(0.074)	0.526	(0.105)	0.88
c_2	−0.164	(0.122)	−0.197	(0.130)	0.19
c_3	−0.137	(0.243)	−0.080	(0.252)	0.82
c_4	−0.611	(0.883)	−0.488	(1.449)	0.35

TABLE III
CLASSIFICATION PERFORMANCES IN % USING THE α SET OF EXPONENTS ESTIMATED OVER 4 OCTAVES

Center scale (s)	Accuracy	Sensitivity	Specificity	N. Feature
1.71	63.02	46.03	80.00	3
3.41	54.05	71.43	36.67	15
6.83	58.02	79.37	36.67	28
13.7	67.90	80.95	54.84	2
27.3	**72.66**	**90.48**	**54.84**	**30**
54.6	64.52	77.42	51.61	18
109.2	57.26	72.58	41.94	2
218.5	62.90	77.42	48.39	2

Bold indicates best accuracy set.

TABLE IV
CLASSIFICATION PERFORMANCES IN % USING THE β SET

Scale (s)	Accuracy	Sensitivity	Specificity	N. Feature
0.21	60.93	44.44	77.42	15
0.43	67.95	74.60	61.29	39
0.85	68.66	85.71	51.61	28
1.71	67.90	80.95	54.84	29
3.41	66.26	84.13	48.39	29
6.83	**79.11**	**90.48**	**67.74**	**4**
13.7	63.06	80.95	45.16	12
27.3	71.86	88.89	54.84	14
54.6	58.22	80.95	35.48	17
109	64.70	77.78	51.61	11
218	63.36	42.86	83.87	1
437	71.07	87.30	54.84	31
874	61.75	42.86	80.65	1
1748	67.13	76.19	58.06	21
3495	77.44	96.83	58.06	31

Bold indicates best accuracy per feature set.

Yet, none of the exponents c_m, considered individually, can be directly translated into the clinical practice for risk stratification between NS and SV. Consistently with the fact that autonomic nervous system linear and nonlinear dynamics cannot be fully explained by a single measure only, in the next paragraph we show how to combine the aforementioned multifractal point-process measures for SV vs. NS discrimination in CHF at a single subject level.

C. SV Versus NS Classification

Leveraging on the aforementioned results performed at a group-wise level and with inferential significance only, we moved beyond statistical analysis to automatically discern SV from NS patients with CHF at a single-subject level. Scaling and multifractal features of point process-derived heartbeat dynamics are then combined throughout a nonlinear discriminant function, allowing therefore for a direct clinical translation. Following the methodology description, we considered instantaneous dynamics of $\mu_{RR}(t)$, $\xi_0(t)$, $\sigma^2_{RR}(t)$, $\sigma^2_{HR}(t)$, $VLF(t)$, $LF(t)$, $HF(t)$, $LF/HF(t)$, and condensed the information about the long-term, time-varying dynamics using the α and β sets of exponents and multiscale representations defined in Section II-D.

Throughout the LOO-SVM procedure, prediction accuracy, sensitivity and specificity in discerning SV vs. NS patients were evaluated for feature sets α and β, whose results are shown in Tables III and IV, respectively. For each scale, these tables report the best classification accuracy using a proper combination of features, as identified by the SVM-RFE algorithm. Considering the two CHF classes, accuracy of 50% is the change.

Using the subset of exponents $\zeta(2)$, c_1, c_2, c_3, c_4, an accuracy of 72.66% was obtained for exponents estimated over scales 27.3 s $\pm$ 2 octaves. Nevertheless, specificity was barely beyond the chance level (54.84%), being therefore not suitable for an actual clinical application.

Using the subset of multiscale representation $\log_2 S(2, j)$, $C_1(j)$, $C_2(j)$, $C_3(j)$, $C_4(j)$, best classification accuracy of 79.11% was obtained at scale 6.83 s, with satisfactory sensitivity of 90.48% and specificity 67.74%. The trend of classification accuracy as a function of the number of features is shown in Fig. 4. Particularly, the following four features were selected as best candidate for the prediction of survivors in patients with CHF: $\log_2 S(2, j)$, $C_3(j)$, $C_4(j)$ calculated over $VLF(t)$, and $\log_2 S(2, j)$ calculated over $LF/HF(t)$, at scale $j = 10$ ($\sim$7 s) at which the precise choice of interpolation (here, using the informative point process model) has significant impact.

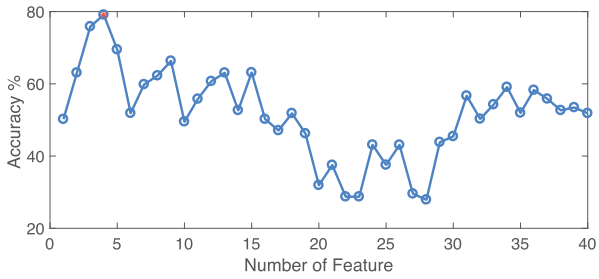

Fig. 4. Recognition accuracy in discerning NS vs. SV patients as a function of the feature rank estimated through the SVM-RFE procedure, considering feature set β comprising $\log_2 S(2,j)$, $C_1(j), C_2(j), C_3(j), C_4(j)$ at scale 6.83 s.

Merging the proposed multifractal features of α and β sets did not straightforwardly improve the aforementioned best classification accuracy of 79.11%.

IV. Discussion and Conclusion

We proposed a novel methodology combining multifractal analysis with instantaneous (time resolution of 5 ms) physiological estimates derived from inhomogeneous point-process models of cardiovascular dynamics. As previous evidences demonstrated that autonomic nervous system dynamics affects heartbeat complexity at all scales [33], we hypothesized that our methodology would provide a good predictor of mortality following congestive heart failure with single-patient specific prognostic capabilities.

All instantaneous series derived from our physiologically-informative model show a clear scaling behaviour at coarser scales over all indices of self-similarity and multifractality. Conversely, considering multifractal indices $C_2(j), C_3(j), C_4(j)$ for the scales $\sim 2-10$ s, the scaling behaviour of spline-interpolated series of *RR* intervals is broken and departs from the behaviour observed at scales $\geq$10 s. This is particularly evident for multifractal index $C_4(j)$. Note that self-similar models describe only parts of the scaling properties of the heartbeat interval series, whereas multifractal models provide a more comprehensive description (e.g., [2], [8]). Therefore, we demonstrated that scaling and multiscale representations of *RR* interval series is biased by the interpolating method employed (e.g., linear, spline, etc.). Therefore, more informative ad-hoc physiologically plausible models, such as the inhomogeneous point-process [14], [25], are strongly recommended. This result is in agreement with our previous investigations [14], [25] demonstrating that the use of an inverse-Gaussian distribution, characterized at each moment in time, inherits both physiological (the integrate-and-fire initiating the cardiac contraction [25]) and methodological information.

Additionally, we found that series of purely vagal dynamics, i.e., $HF(t)$, display power law scaling from $\sim$0.5 s to $\sim$82 s, whereas series of sympatho-vagal dynamics (e.g., $LF(t)$ and $LF/HF(t)$) are associated with scale invariance in form of power laws exclusively for scales larger than $\sim$100 s. This is also in agreement with previous evidences reporting that sympathetic activity affects complexity at long time scales [33] only. Scaling and multifractal properties of circadian heartbeat dynamics in CHF patients, therefore, do not arise at a sinus-node level, but seem to be already intrinsically present in vagal and sympatho-vagal dynamics. At a speculative level, this can be due to dysfunctional acetylcholine release on adrenergic receptors on the vagal terminals, and/or dysfunctional cytosolic adenosine 3,5-cyclic monophosphate release in post-junctions, and/or dysfunctional acetylcholine release on muscarinic receptors [1].

Using these measures, we were able to predict survivor and non-survivor CHF patients (4 year follow-up) with a satisfactory accuracy of 79.11% (sensitivity 90.48% and specificity 67.74%), considering newly-derived heartbeat variables. To the best of our knowledge, the majority of the previous studies dealing with CHF mortality prediction evaluated the predictive power of novel HRV markers using p-values and statistical inference only. Since results from statistical inference refer to a group-level analysis, whereas our classification results deal with single subject-level analysis, a proper comparison of the proposed multifractal point-process methodology with these studies cannot be performed. To give an idea of the significance of our results, here we mention few studies that quantified accuracy, specificity, and sensitivity of an HRV- based methodology for the mortality prediction in CHF. In particular, our results show higher statistical performances than Yang *et al.* (accuracy: 74.4%) [34], Bigger *et al.* (sensitivity 58%, specificity of 71%) [35], and are comparable with Pecchia *et al.* (79.3%) [36]. An indirect quantitative reference to our results with other relevant reports would point at an accuracy rate lower than Melillo *et al.* (85.4%) [37], Guidi *et al.* (86%, sensitivity and sensibility not reported) [38], and Shahbazi *et al.* (100%) [39], although Melillo *et al.*'s method is with a specificity rate of 63.6%, and results from Melillo *et al.*, Guidi *et al.*, and Shahbazi *et al.* are from 41, 50, and 44 patients, respectively. Here, it is important to highlight again that our study is associated with a significantly higher statistical power than others, given our sample of 94 patients. Also, it must be noted that methods proposed by Guidi *et al.* [38], and Yang *et al.* [34] need some parameters as input that should be gathered directly from physicians, while the adoption of only HRV measures, as in the current study, enables a completely automatic assessment.

We found that optimal predictors of mortality in this kind of pathology are associated with multifractal quantification of very low frequency oscillations ($<$0.04 Hz) of heartbeat dynamics. Although precise physiological correlates of such VLF are not well-defined yet [4], it is reasonable to associate proper diagnostic and prognostic value to multifractal changes in cardiovascular nonlinear oscillations with period between 25 s and 100 s. Accordingly, other studies involving circadian cardiovascular rhythms or long-term sleep recordings highlighted such clinical value of VLF dynamics, also as a powerful predictor of clinical prognosis in patients with CHF [40]–[44]. In particular, testing on a large cohort of asymptomatic participants undergoing 24 h Holter ECG recordings, the short-term fractal scaling exponent of heartbeat dynamics and VLF power have been recently selected as best candidate for the prediction of CHF onset on follow-up [44]. To this extent, using the same standard clinical recordings, our study makes a scientific step

forward, providing an effective methodology predicting mortality in CHF within a 4 years period at a single-patient level.

The number of subjects (94) has provided solid ground for validation of our multifractal framework. Nevertheless, we are planning a new prospective clinical trial study devoted to the collection of long-term cardiovascular data from CHF patients, including mortality follow-up evaluations. Moreover, we are aware that the classification results shown in Tables III and IV cannot be considered "optimal". While in the initial phases of this study we performed some exploratory analyses including different classifiers such as Linear and Quadratic Discriminant Classifiers, K-Nearest Neighbors, Artificial Neural Network, and others, a rigorous/unbiased comparison between classifiers would require proper parameter optimization to be performed at each step of the leave one out procedure within a nested-cross validation framework, which should also include parameter optimization for each classifier. This kind of optimization would call for a larger sample size (see limitation above) and, most importantly, is beyond the scope of this study, whose primary aim is to demonstrate that novel multifractals for inhomogeneous point-process models carry very discriminant power and are associated with prediction of CHF mortality. Indeed, the obtained accuracy, with associated specificity and sensitivity, may increase with a proper optimization of the classification algorithm. Future works will also focus on the investigation of combined scaling and multifractal analysis, and instantaneous nonlinear/complex heartbeat dynamics including time-varying bispectra [14], time-varying Lyapunov spectra [45], and time-varying monovariate and multivariate cardiac entropy [16], [46], extending therefore to higher-order statistics the recently proposed *complexity variability* framework [45] (which is currently defined through second-order moments).

In conclusion, this study poses a solid methodological basis for devising a tool capable of performing accurate assessments of CHF morbidity and sudden mortality, which still remain unacceptably high despite effective ongoing drug therapies. We suggest that, in case of severe CHF, dysfunctional, multidimensional power-law scaling of instantaneous sympatho-vagal dynamics, as estimated through physiologically-plausible probabilistic models of heartbeat generation, should be considered as a high-mortality risk factor in a 4-year follow-up.

REFERENCES

[1] K. Sunagawa *et al.*, "Dynamic nonlinear vago-sympathetic interaction in regulating heart rate," *Heart vessels*, vol. 13, no. 4, pp. 157–174, 1998.

[2] P. C. Ivanov *et al.*, "Multifractality in human heartbeat dynamics," *Nature*, vol. 399, no. 6735, pp. 461–465, 1999.

[3] C. Schäfer *et al.*, "Heartbeat synchronized with ventilation," *Nature*, vol. 392, no. 6673, pp. 239–240, 1998.

[4] U. R. Acharya *et al.*, "Heart rate variability: A review," *Med. Biol. Eng. Comput.*, vol. 44, no. 12, pp. 1031–1051, 2006.

[5] Y. Yamamoto and R. L. Hughson, "On the fractal nature of heart rate variability in humans: Effects of data length and beta-adrenergic blockade," *Amer. J. Physiol.-Regulatory, Integrative Comparative Physiol.*, vol. 266, no. 1, pp. R40–R49, 1994.

[6] T. Nakamura *et al.*, "Multiscale analysis of intensive longitudinal biomedical signals and its clinical applications," *Proc. IEEE*, vol. 104, no. 2, pp. 242–261, Feb. 2016.

[7] G. Captur *et al.*, "The fractal heart—embracing mathematics in the cardiology clinic," *Nature Rev. Cardiology*, vol. 14, pp. 56–64, 2017.

[8] M. Doret *et al.*, "Multifractal analysis of fetal heart rate variability in fetuses with and without severe acidosis during labor," *Amer. J. Perinatol.*, vol. 28, no. 4, pp. 259–266, 2011.

[9] K. Kiyono *et al.*, "Non-gaussian heart rate as an independent predictor of mortality in patients with chronic heart failure," *Heart Rhythm*, vol. 5, no. 2, pp. 261–268, 2008.

[10] H. Wendt *et al.*, "Bootstrap for empirical multifractal analysis," *IEEE Signal Proc. Mag.*, vol. 24, no. 4, pp. 38–48, Jul. 2007.

[11] H. Wendt *et al.*,, "Multiscale wavelet p-leader based heart rate variability analysis for survival probability assessment in CHF patients," in *Proc. Int. IEEE EMBS Conf.*, Chicago, USA, 2014, pp. 2809–2812.

[12] M. Costa, A. L. Goldberger, and C.-K. Peng, "Multiscale entropy analysis of complex physiologic time series," *Phys. Rev. Lett.*, vol. 89, no. 6, 2002, Art. no. 068102.

[13] D. Bansal *et al.*, "A review of measurement and analysis of heart rate variability," *Int. Conf. Comput. Autom. Eng.*, pp. 243–246, 2009.

[14] G. Valenza *et al.*, "Point-process nonlinear models with Laguerre and Volterra expansions: Instantaneous assessment of heartbeat dynamics," *IEEE T. Signal Proc.*, vol. 61, no. 11, pp. 2914–2926, Jun. 2013.

[15] R. Maestri *et al.*, "Nonlinear indices of heart rate variability in chronic heart failure patients: Redundancy and comparative clinical value," *J. Cardiovascular Electrophysiology*, vol. 18, no. 4, pp. 425–433, 2007.

[16] G. Valenza *et al.*, "Inhomogeneous point-process entropy: An instantaneous measure of complexity in discrete systems," *Phys. Rev. E*, vol. 89, no. 5, 2014, Art. no. 052803.

[17] G. Valenza *et al.*, "Estimation of instantaneous complex dynamics through lyapunov exponents: A study on heartbeat dynamics," *PloS one*, vol. 9, no. 8, 2014, Art. no. e105622.

[18] T. H. Mäkikallio *et al.*, "Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure," *Amer. J. Cardiol.*, vol. 87, no. 2, pp. 178–182, 2001.

[19] K. Kiyono *et al.*, "Critical scale-invariance in healthy human heart rate," *Phys. Rev. Lett.*, vol. 93, 2004, Art. no. 178103.

[20] R. Sassi *et al.*, "Multifractality and heart rate variability," *Chaos, Interdisciplinary J. Nonlinear Sci.*, vol. 19, no. 2, 2009, Art. no. 028507.

[21] S. Dutta, "Multifractal properties of ECG patterns of patients suffering from congestive heart failure," *J. Statistical Mech., Theory Exp.*, vol. 2010, no. 12, 2010, Art. no. P12021.

[22] R. Galaska *et al.*, "Comparison of wavelet transform modulus maxima and multifractal detrended fluctuation analysis of heart rate in patients with systolic dysfunction of left ventricle," *Ann. Noninvasive Electrocardiology*, vol. 13, no. 2, pp. 155–164, 2008.

[23] J. Nolan *et al.*, "Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial," *Circulation*, vol. 98, pp. 1510–1516, 1998.

[24] T. Mäkikallio *et al.*, "Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure," *Amer. J. Cardiol.*, vol. 87, pp. 178–182, 2001.

[25] R. Barbieri *et al.*, "A point-process model of human heartbeat intervals: new definitions of heart rate and heart rate variability," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 288, no. 1, pp. H424–H435, 2005.

[26] R. Leonarduzzi *et al.*, "p-exponent and p-leaders, part ii: Multifractal analysis. relations to detrended fluctuation analysis." *Physica A*, vol. 448, pp. 319–339, 2016.

[27] G. Valenza *et al.*, "Point-process high-resolution representations of heartbeat dynamics for multiscale analysis: A CHF survivor prediction study," in *Proc. 37th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, 2015, pp. 1951–1954.

[28] G. Valenza *et al.*, "Multiscale properties of instantaneous parasympathetic activity in severe congestive heart failure: A survivor vs non-survivor study," in *Proc. 39th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.,* 2017, pp. 3761–3764.

[29] L. Citi *et al.*, "A real-time automated point-process method for the detection and correction of erroneous and ectopic heartbeats," *IEEE Trans. Biomed. Eng.*, vol. 59, no. 10, pp. 2828–2837, Oct. 2012.

[30] S. Mallat, *A Wavelet Tour of Signal Processing*. Cambridge, MA, USA: Academic press, 1999.

[31] K. Yan and D. Zhang, "Feature selection and analysis on correlated gas sensor data with recursive feature elimination," *Sens. Actuators B: Chemical*, vol. 212, pp. 353–363, 2015.

[32] C.-C. Chang and C.-J. Lin, "Libsvm: A library for support vector machines," *ACM Trans. Intell. Syst. Technol.* , vol. 2, no. 3, 2011, Art. no. 27.

[33] L. E. V. Silva *et al.*, "The role of sympathetic and vagal cardiac control on complexity of heart rate dynamics," *Amer. J. Physiol.-Heart Circulatory Physiol.*, vol. 312, no. 3, pp. H469–H477, 2017.

[34] G. Yang *et al.*, "A heart failure diagnosis model based on support vector machine," in *Proc. 3rd Int. Conf. Biomed. Eng. Informat.,* 2010, vol. 3., pp. 1105–1108.
[35] J. T. Bigger *et al.*, "Frequency domain measures of heart period variability and mortality after myocardial infarction." *Circulation*, vol. 85, no. 1, pp. 164–171, 1992.
[36] L. Pecchia *et al.*, "Remote health monitoring of heart failure with data mining via cart method on HRV features," *IEEE Trans. Biomed. Eng.*, vol. 58, no. 3, pp. 800–804, Mar. 2011.
[37] P. Melillo *et al.*, "Classification tree for risk assessment in patients suffering from congestive heart failure via long-term heart rate variability," *IEEE J. Biomed. Health Informat.*, vol. 17, no. 3, pp. 727–733, May 2013.
[38] G. Guidi *et al.*, "Heart failure artificial intelligence-based computer aided diagnosis telecare system," *Int. Conf. Smart Homes Health Telematics*, 2012, pp. 278–281.
[39] F. Shahbazi and B. M. Asl, "Generalized discriminant analysis for congestive heart failure risk assessment based on long-term heart rate variability," *Comput. Methods Programs Biomed.*, vol. 122, no. 2, pp. 191–198, 2015.
[40] L. Bernardi *et al.*, "Physical activity influences heart rate variability and very-low-frequency components in holter electrocardiograms," *Cardiovascular Res.*, vol. 32, no. 2, pp. 234–237, 1996.
[41] T. Shiomi *et al.*, "Augmented very low frequency component of heart rate variability during obstructive sleep apnea," *Sleep*, vol. 19, no. 5, pp. 370–377, 1996.
[42] M. Hadase *et al.*, "Very low frequency power of heart rate variability is a powerful predictor of clinical prognosis in patients with congestive heart failure," *Circulation J.*, vol. 68, no. 4, pp. 343–347, 2004.
[43] A. Tamura *et al.*, "Association between the severity of obstructive sleep apnea and very low frequency powers in frequency domain analysis of heart rate variability," in *Eur. Heart J.*, vol. 37, pp. 263–264, 2016.
[44] V. N. Patel *et al.*, "Association of holter-derived heart rate variability parameters with the development of congestive heart failure in the cardiovascular health study," *JACC: Heart Failure*, vol. 5, no. 6, pp. 423–431, 2017.
[45] G. Valenza *et al.*, "Complexity variability assessment of nonlinear time-varying cardiovascular control," *Sci. Rep.*, vol. 7, 2017, Art. no. 42779.
[46] G. Valenza *et al.*, "Instantaneous transfer entropy for the study of cardiovascular and cardio-respiratory nonstationary dynamics," *IEEE Trans. Biomed. Eng.*, vol. 65, no. 5, pp. 1077–1085, May 2018.