

# “Summer Shift”: A Potential Effect of Sunshine on the Time Onset of ST-Elevation Acute Myocardial Infarction

Carlo Vittorio Cannistraci, Eng, PhD; Tuomo Nieminen, MD, PhD; Masahiro Nishi, MD; Levon M. Khachigian, PhD, DSc; Juho Viikilä, MD; Mika Laine, MD, PhD; Domenico Cianflone, MD; Attilio Maseri, MD; Khung Keong Yeo, MBBS; Ravinay Bhandi, MBBS, PhD; Enrico Ammirati, MD, PhD

**Background**—ST-elevation acute myocardial infarction (STEMI) represents one of the leading causes of death. The time of STEMI onset has a circadian rhythm with a peak during diurnal hours, and the occurrence of STEMI follows a seasonal pattern with a salient peak of cases in the winter months and a marked reduction of cases in the summer months. Scholars investigated the reason behind the winter peak, suggesting that environmental and climatic factors concur in STEMI pathogenesis, but no studies have investigated whether the circadian rhythm is modified with the seasonal pattern, in particular during the summer reduction in STEMI occurrence.

**Methods and Results**—Here, we provide a multiethnic and multinational epidemiological study (from both hemispheres at different latitudes, n=2270 cases) that investigates whether the circadian variation of STEMI onset is altered in the summer season. The main finding is that the difference between numbers of diurnal (6:00 to 18:00) and nocturnal (18:00 to 6:00) STEMI is markedly decreased in the summer season, and this is a prodrome of a complex mechanism according to which the circadian rhythm of STEMI time onset seems season dependent.

**Conclusions**—The “summer shift” of STEMI to the nocturnal interval is consistent across different populations, and the sunshine duration (a measure related to cloudiness and solar irradiance) underpins this season-dependent circadian perturbation. Vitamin D, which in our results seems correlated with this summer shift, is also primarily regulated by the sunshine duration, and future studies should investigate their joint role in the mechanisms of STEMI etiology. (*J Am Heart Assoc.* 2018;7:e006878. DOI: 10.1161/JAHA.117.006878.)

**Key Words:** chronobiology • circadian rhythm • epidemiology • risk factor • seasonal variation • ST-segment elevation myocardial infarction

ST-elevation acute myocardial infarction (STEMI) represents 1 of the leading causes of death<sup>1</sup> and is mainly due to acute atherothrombotic occlusion of a coronary artery causing myocardial ischemia and necrosis.<sup>2,3</sup> Triggers that explain this acute transition from asymptomatic coronary plaques to acute thrombosis and STEMI are still under

investigation.<sup>2,3</sup> The fact that onset of STEMI has a circadian rhythm with a peak during diurnal hours has been well described.<sup>4-12</sup> A seasonal pattern<sup>13</sup> in the occurrence of STEMI was also found with a salient peak of cases in the winter months and a marked nadir of cases in the summer months.<sup>14-19</sup> Several studies have investigated the reason

From the Biomedical Cybernetics Group, Biotechnology Center (BIOTEC), Center for Molecular and Cellular Bioengineering (CMCB), Center for Systems Biology Dresden (CSBD), Department of Physics, Technische Universität Dresden, Dresden, Germany (C.V.C.); Brain Bio-Inspired Computing (BBC) Lab, IRCCS Centro Neurolesi “Bonino Pulejo”, Messina, Italy (C.V.C.); Internal Medicine (T.N.) and Cardiology (J.V., M.L.), University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; South Karelia Central Hospital, Lappeenranta, Finland (T.N.); Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan and Department of Cardiology, Omihachiman Community Medical Center, Omihachiman, Japan (M.N.); Vascular Biology and Translational Research, School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia (L.M.K.); San Raffaele Vita-Salute University and Hospital, Milan, Italy (D.C.); Heart Care Foundation, Florence, Italy (A.M.); National Heart Centre Singapore, Singapore (K.K.Y.); Royal North Shore Hospital, Sydney, Australia (R.B.); De Gasperis Cardio Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy (E.A.).

**Correspondence to:** Carlo Vittorio Cannistraci, PhD, Biomedical Cybernetics Group, Biotechnology Center (BIOTEC), Center for Molecular and Cellular Bioengineering (CMCB), Technische Universität Dresden (TUD)-Tatzberg 47/49, 01307 Dresden, Germany. E-mail: kalokagathos.agon@gmail.com  
 Enrico Ammirati, MD, PhD, De Gasperis Cardio Center and Transplant Center, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milano, Italy. E-mail: enrico.ammirati@ospedaleniguarda.it

Received June 7, 2017; accepted February 14, 2018.

© 2018 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

## Clinical Perspective

### What Is New?

- In summer the time of ST-elevation acute myocardial infarction onset shifts significantly to the nocturnal interval (18:00-6:00).
- This summer shift seems associated with sunshine duration, a measure related to cloudiness and solar irradiance duration.
- This study suggests that seasonal rhythms associated with sunshine duration may influence circadian rhythms of ST-elevation acute myocardial infarction onset.

### What Are the Clinical Implications?

- Future studies should consider investigating the molecular mechanisms that link sunshine duration to seasonal/circadian variability of ST-elevation acute myocardial infarction onset.

behind the winter peak and suggested that STEMI is more common in winter and more common on colder days, independent of season.<sup>20,21</sup> Thus, environmental and climatic factors may play an important part in STEMI pathogenesis, although the role of seasonal dependency per se is still unclear. In general, the influence of seasonal pattern over circadian rhythm in STEMI onset is still an open topic, and, surprisingly, no studies have investigated whether changes in circadian variations were correlated with the nadir during the summer season and the environmental factors that may be at the root of this correlation. Here, for the first time, we provide a multiethnic and multination epidemiological study that considers patients from both hemispheres at different latitudes, and we investigate whether changes in circadian variations are associated with the seasonal nadir during the summer.

## Methods

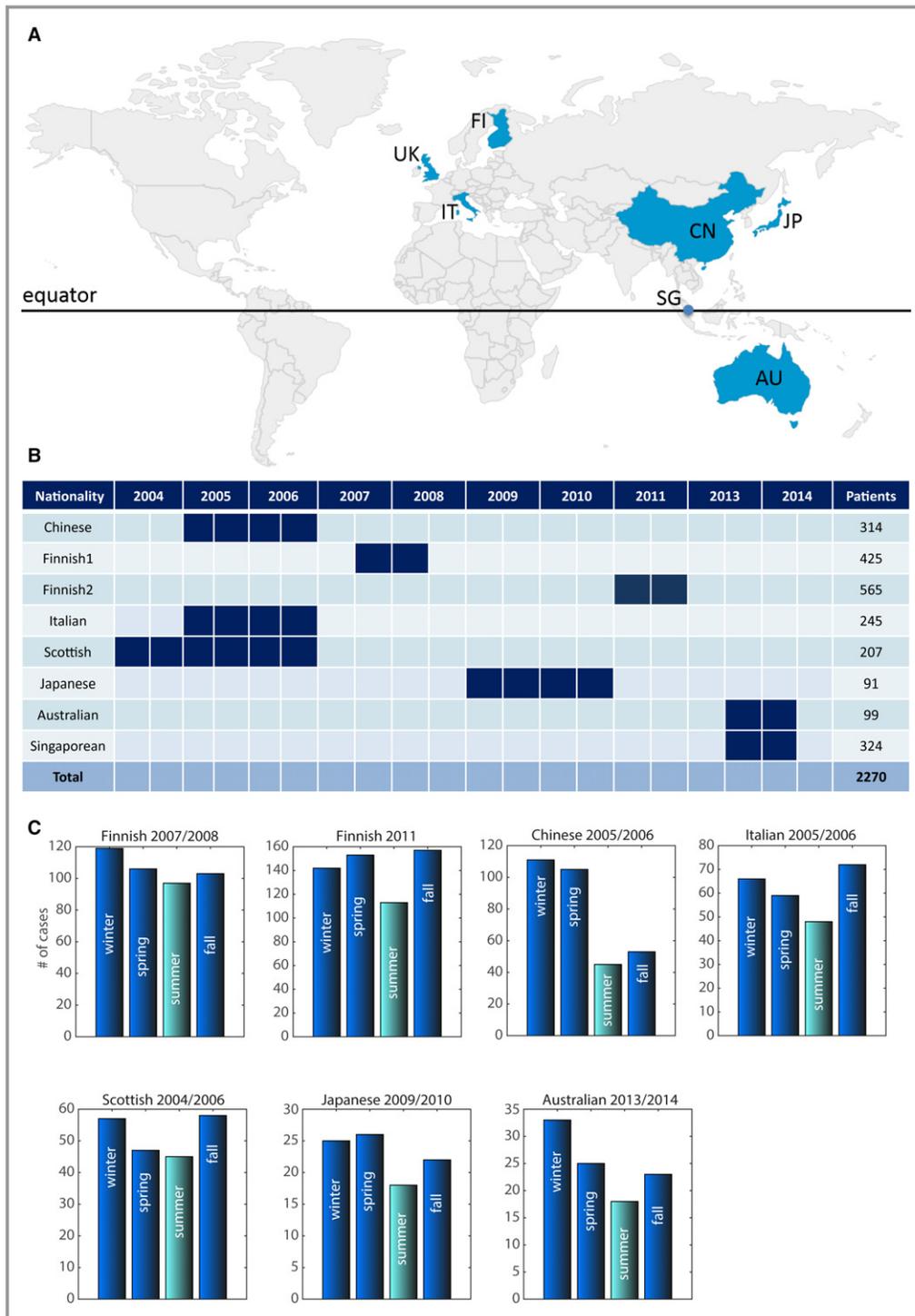
### Study Design

Patient recruitment was approved by the respective institutional review committees, and the subjects gave informed consent. Data can be made available to other researchers by request to the corresponding author.

In this multiethnic and multicenter study, we considered a total of 2270 STEMI patients from 7 countries (Figure 1A) in both hemispheres at different latitudes, including 3 multicenter national registers from the prospective FAMI (First Myocardial Infarction) study conducted in Italy, China, and Scotland<sup>22</sup>; 2 multicenter national registers from the prospective Finnish (HUS-STEMI I-II) studies<sup>23</sup>; and 3 single-center registers from

Japan, Australia, and Singapore. Figure 1A offers an overview of the population samples considered in our study, together with the range of years in which STEMI patients were included in the study (Figure 1B). In Table 1 age, female prevalence, and potential confounders of circadian rhythm of STEMI (ie, diabetic status, taking  $\beta$ -blockers or aspirin before STEMI) of the patient populations considered in this study were reported when available. The included patients from China, Italy, and Scotland derive from the published multiethnic FAMI study. They were consecutive prospectively recruited patients with STEMI as the first manifestation of coronary disease. All patients provided written informed consent. Details on the FAMI study and characteristics of the entire population are reported by Cristell et al<sup>22</sup> and Ammirati et al.<sup>24</sup> For the Finnish population, we considered 2 published data sets<sup>23</sup> collected in Helsinki University Central Hospital starting in 2007 (HUS-STEMI I) and 2011 (HUS-STEMI II), and there was a further extension in the number of participants included in these 2 registries. In the Japanese registry (unpublished data), mean ( $\pm$ SD) age in men was  $65\pm 12$  years and in women  $76\pm 12$  years with a male prevalence of 81%. Patients on  $\beta$ -blockers at onset of STEMI were as low as 2%, and on aspirin 12%. In the Australian population (unpublished data), the mean age ( $\pm$ SD) was  $62\pm 19$  years, and male prevalence was 76% with a use of  $\beta$ -blockers before the admission for STEMI of 9%, and of aspirin 20%. The prevalence of diabetic patients was 10%. In the Singaporean population (unpublished data), the mean age ( $\pm$ SD) was  $60\pm 12$  years, male prevalence was 81%, and no data were available for diabetes mellitus and treatments before STEMI.

Inclusion criteria for our study (whose population features are shown in Figure 1 and Table 1) were very restrictive. First, to avoid missing information bias, we considered only data sequences presenting individuals without monthly interruption over a continuous range of 12 months. Second, we were interested in setting a criterion to prefilter populations (data sequences) that were definitely incorrectly sampled. Prior studies<sup>14-19</sup> established that a correctly sampled STEMI population always shows a seasonal pattern with a summer nadir with respect to the remainder of the year. Hence, we decided to prefilter the data for reliability by accepting only populations that did not show higher occurrence of STEMI in summer months with respect to the average seasonal value during the rest of the year. This still did not insure that the populations that passed the prefiltering displayed a summer nadir because, for example, a population with occurrence of STEMI in the summer equal to the average seasonal value during the rest of the year would pass the prefilter. However, this represented a reasonable first stage to prefilter populations that were affected by a clear sign of poor reliability. The next step was to ensure that all the populations that passed the prefiltering were actually displaying a summer nadir.



**Figure 1.** A, Map highlighting the enrolled countries B, Population and years of inclusion. Note: no patients were included in 2012. C, Seasonal pattern in STEMI onset.

Figure 1C provides a confirmation that a seasonal pattern with summer nadir characterizes all the populations accurately prefiltered and included in our analysis. Therefore, we decided to investigate (Figure 2) whether the clear overall decrease of STEMI onset during summer (summer nadir) would also affect the circadian peak during the diurnal hours

(second and third quarter of the day, 6:00 to 18:00) with respect to the nocturnal hours (the fourth and first quarter of the day, 18:00 to 6:00). The choice to select these 2 precise intervals (6:00 to 18:00 and 18:00 to 6:00) was motivated by the fact that this subdivision was largely accepted in previous studies, and in general, higher incidence of STEMI occurs

**Table 1.** Age, Sex, and Prevalence of Potential Confounders on Circadian Rhythms in the Populations Included in the Study

	Finland1	Finland2	China	Italy	Scotland	Japan	Australia	Singapore
N	425	565	314	245	207	91	99	324
Age (y), mean±SD	64±12	64±13	61±13	61±11	61±12	70±13	62±19	60±12
Female, N (%)	138 (32)	154 (27)	63 (20)	56 (23)	58 (28)	18 (20)	24 (24)	62 (19)
Diabetes mellitus, %	18	NA	NA	NA	NA	22	10	NA
β-Blockers, %	NA	NA	3	9	12	2	9	NA
Aspirin, %	NA	NA	9	21	20	12	20	NA

In the first column of the table (which specifies the considered feature) the letter, N is in the first row for number of the population's individuals and in the third row for number of females. The features β-blockers and aspirin refer to treatment before STEMI. NA indicates not available.

during the second and third quarters of the day.<sup>4-9</sup> Hence, we decided to measure the percentage difference (Δ%) of STEMI onset during the 6:00 to 18:00 (diurnal) interval with respect to the 18:00 to 6:00 (nocturnal) interval using the following formula:

$$\Delta\% = \frac{(\#STEMI \text{ in } 6 \text{ to } 18 \text{ time interval}) - (\#STEMI \text{ in } 18 \text{ to } 6 \text{ time interval})}{(\#STEMI \text{ in } 18 \text{ to } 6 \text{ time interval})} \times 100$$

### Correlation of Δ% Signal With Climatic Indicators and Vitamin D Levels

The monthly values (yearly averages) of the climatic indicators adopted for computing the correlations in the Singapore population (Figure 3B) are reported together with the references in Table 2. For Figure 3A, we computed the Δ% directly for each 2-month interval (referring to the sum of events happening in the considered 2 months in the 6:00-to-18:00 and the 18:00-to-6:00 intervals separately). For Figure 3B, we computed the average climate indicators for each 2-month interval, and we performed a Spearman correlation between the bimonthly Δ% and the bimonthly climatic indicator signals. The Spearman correlation was preferred to the Pearson correlation because the bimonthly Δ% time series from Singapore presented outliers. We were not able to recover the data on a year-to-year specific basis, so we opted to use the yearly averages. Although using the climatic indicators on a year-to-year basis would improve our analysis, we wish to clarify that using the yearly averages does not invalidate the correctness of our findings.

We applied the same procedure to compute the bimonthly Δ% signal for the overall Finnish (Finnish1+Finnish2=990 total individuals) cohort used in Figure 4. The result was a Spearman correlation −0.71 between the bimonthly Δ% in the overall Finnish cohort and the average bimonthly levels of serum vitamin D in a reference Swedish cohort.<sup>25</sup> The monthly Δ% in the overall Finnish cohort presented noise (see Figure 5) that affected the estimation of the bimonthly Δ%

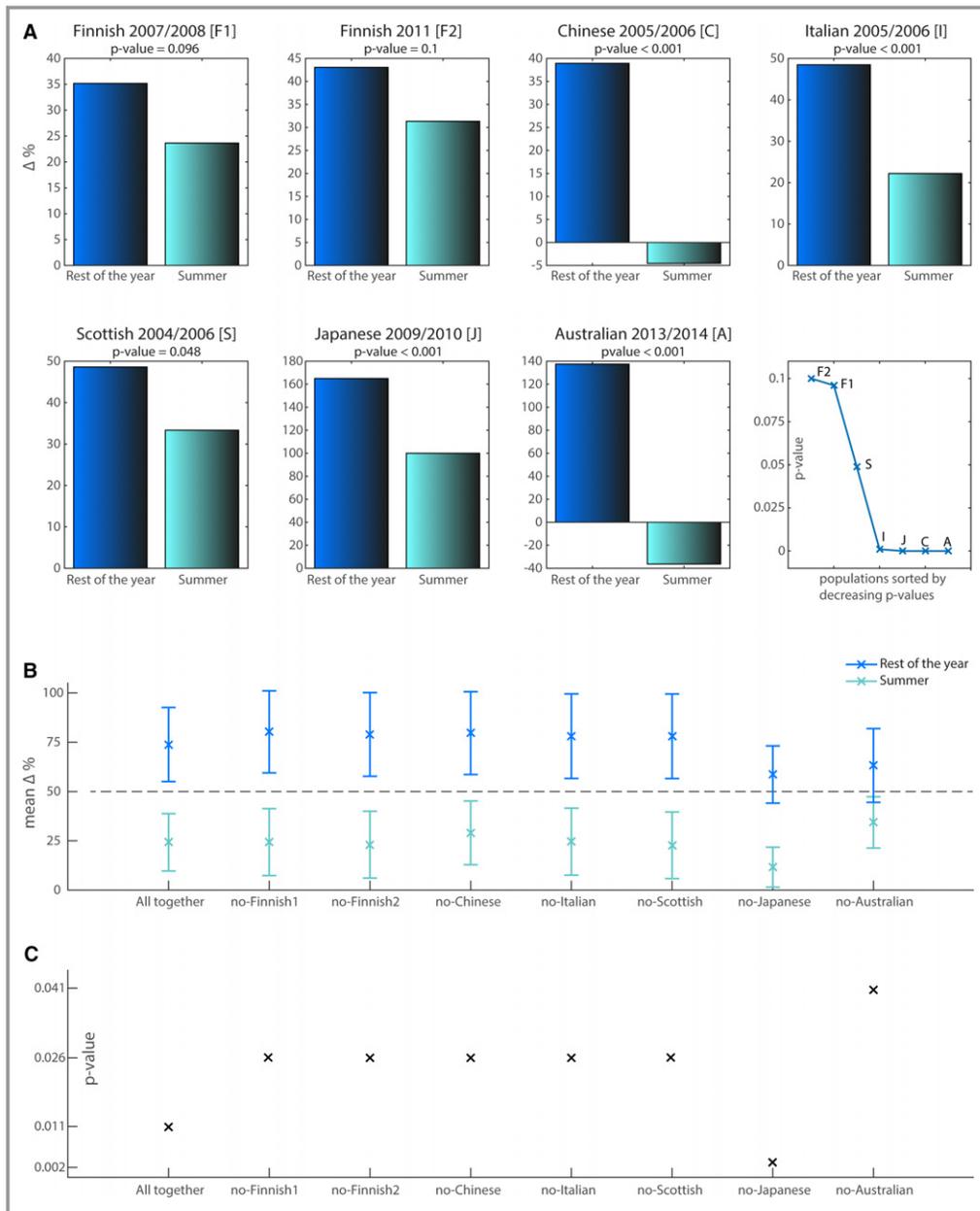
trend used to compute the correlation with bimonthly vitamin D. Therefore, we performed an advanced analysis, and in order to estimate a noise-reduced monthly Δ% time series signal, we applied a nonlinear adaptive filter—the median modified Wiener filter star<sup>26</sup>—for noise reduction and signal

smoothing to the raw monthly Δ% (Figure 5). Then, we computed the noise-reduced bimonthly Δ% signal, using for each 2 months the average of the 2 respective monthly Δ% noise-reduced values; consequently, the Spearman correlation between the noise-reduced bimonthly Δ% signal and bimonthly vitamin D signal increased to −0.77 (Figure 4).

### Results

In Figure 2A, we observed that the difference between diurnal and nocturnal STEMI onset, Δ%, is markedly decreased in the summer season with even a reversal of trend in the Chinese and Australian cohorts. In an unbiased condition we would expect the Δ% to be uniform in summer and in the rest of the year. To evaluate whether the summer reduction significantly deviated from the theoretically expected uniform distribution of observations in the 2 periods, we performed a binomial test. When we plotted the sorted *P*-values (Figure 2A, last plot, bottom right), we noticed that the 2 Finnish populations, although they presented a clear trend (Figure 2A, top left plots), did not show a significant reduction, whereas the Scottish population evinced a significant reduction but with a borderline *P*-value of 0.048. All the other populations presented a highly statistically significant Δ% reduction in the summer season.

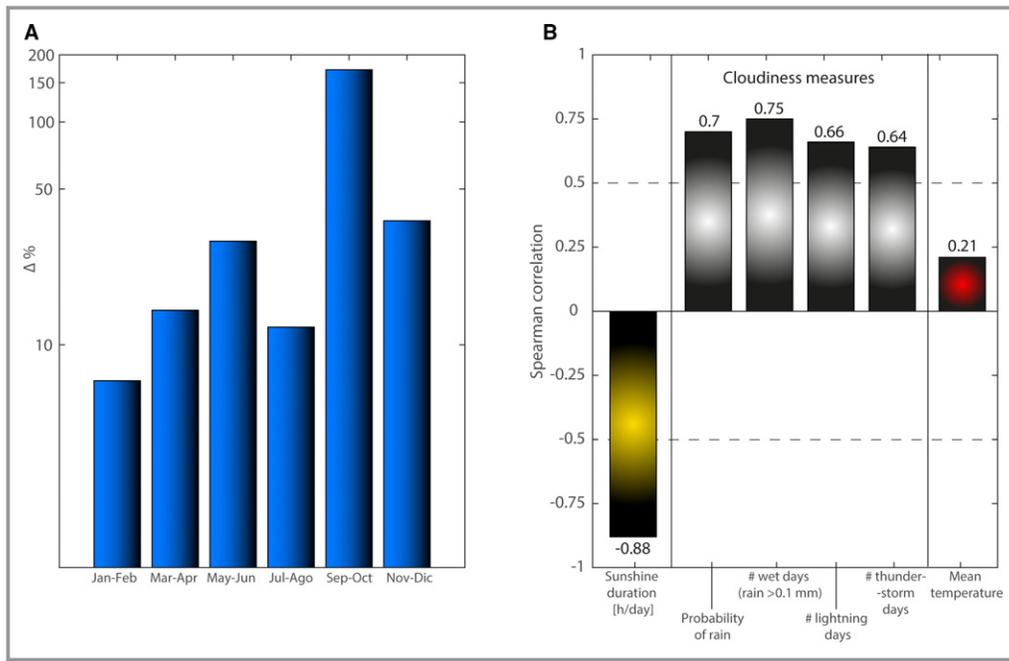
We performed a further analysis to ensure that this summer Δ% reduction is a reliable and robust finding. We plotted the summer Δ% mean and standard error in all the



**Figure 2.** A, Perceptual difference,  $\Delta\%$ , between onset of STEMI in the 6:00 to 18:00 and 18:00 to 6:00 intervals in the summer and in the rest of the year. The bar plot is repeated for each population. The last panel plot is repeated for each population. The population is indicated by the abbreviation in brackets in the title of the bar plots. B, Mean values computed considering the  $\Delta\%$  in summer and in the rest of the year. In order to investigate the significance and robustness of the summer shift, the mean values are computed multiple times adopting a leave-1-out validation that removes 1 population per round and computes the mean values on the remaining ones. The dashed line indicates the reference threshold of 50  $\Delta\%$  for occurrence of summer shift effect. The mean  $\Delta\%$  values are indicated with a cross. For the summer, the crosses are light blue, whereas for the rest of the year the crosses are blue. C, The P-values are the results of a Mann-Whitney test that compares the  $\Delta\%$  values in the summer vs the rest of the year, repeated for each of the leave-1-out-population comparisons reported in b. All the P-values are below the 0.05 threshold.

populations (first point indicated by a cross and error bar in cyan-blue, Figure 2B) and the  $\Delta\%$  mean and standard error in all the populations over the other seasons in the year

(first point indicated by a cross and error bar in the light-blue line, Figure 2B). In addition, to determine whether this result is robust, we removed 1 population per round and



**Figure 3.** A, Bimonthly bar plot of the  $\Delta\%$  trend in the data from Singapore. For better visualization, the  $\Delta\%$  values on the  $y$ -axis are represented using a  $\log_{10}$  transformation. B, Correlation between the  $\Delta\%$  trend and the yearly average values of several climatic indicators.

repeated the same analysis 7 times, creating a plot in which each point was the result obtained by removing the population reported on the  $x$ -axis. The results in Figure 2B clearly indicate that STEMI onset discrepancy between the 6:00-to-18:00 and 18:00-to-6:00 intervals is significantly decreased during the summer with respect to the rest of the year, and this finding is quantitatively supported by the respective significant  $P$ -values (Mann-Whitney test used)

reported in Figure 2C. Only as a visual reference, and with a merely indicative intention, we drew a dashed line at 50  $\Delta\%$  that indicates an empirical distinction between the 2 zones of influence. In addition, we decided to term this evident seasonal effect on the circadian variation the “summer shift” in the time of occurrence of STEMI. The summer-shift hypothesis suggests that in the summer a part of STEMI onset significantly shifts to the 18:00-to-6:00 (nocturnal)

**Table 2.** Climatic Indicators Adopted for Computing the Correlations in Figure 3b

Month	Sunshine Duration (Average Sunlight), h/day	Rain, ppb	Wet (>0.1 mm) Days	Mean Lighting Days	Mean Thunderstorm Days	Mean Temperature (°C)
Jan	6	0.49	17	6	5	27.5
Feb	7	0.23	11	5	6	28.5
Mar	6	0.48	14	14	13	28.5
Apr	6	0.51	15	22	20	28.5
May	6	0.46	15	22	20	29.5
Jun	6	0.46	13	17	15	29
Jul	6	0.47	13	14	13	28
Aug	6	0.48	14	12	14	28
Sep	6	0.46	14	13	15	28.5
Oct	5	0.53	16	20	18	28.5
Nov	5	0.64	18	24	19	28
Dec	4	0.61	19	16	12	27

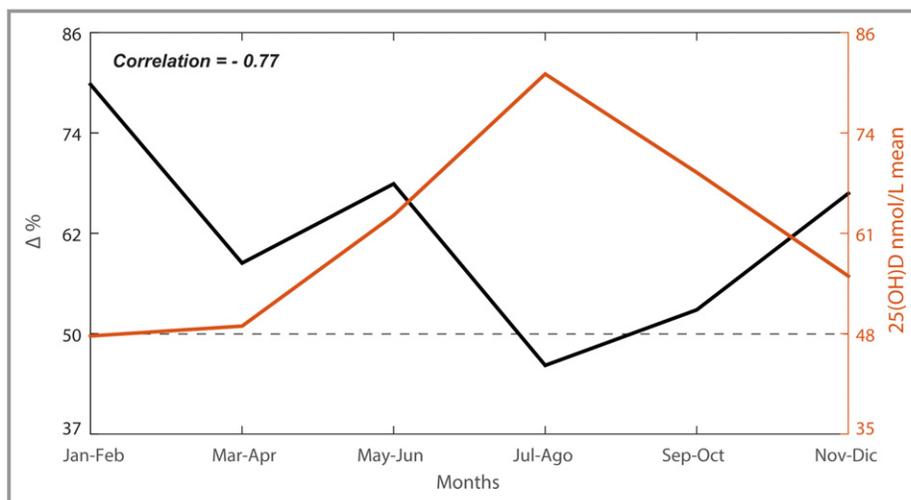
The values are extracted from multiple databases: <http://www.nea.gov.sg/weather-climate>; <http://www.temperatureweather.com/>; <http://www.climatemps.com/>.

interval; and the discrepancy between the numbers of STEMI onsets in the 6:00-to-18:00 (diurnal) interval and the 18:00-to-6:00 (nocturnal) interval is reduced. Interestingly, the plot on the bottom-right of Figure 2A clearly displays that starting from the Finland population and going toward other temperate climate zone populations that are at lower latitudes, the  $P$ -value significance increases. The summer shift is valid for the temperate climate zone and seems to vanish while we progress towards regions at the border with the polar zone.

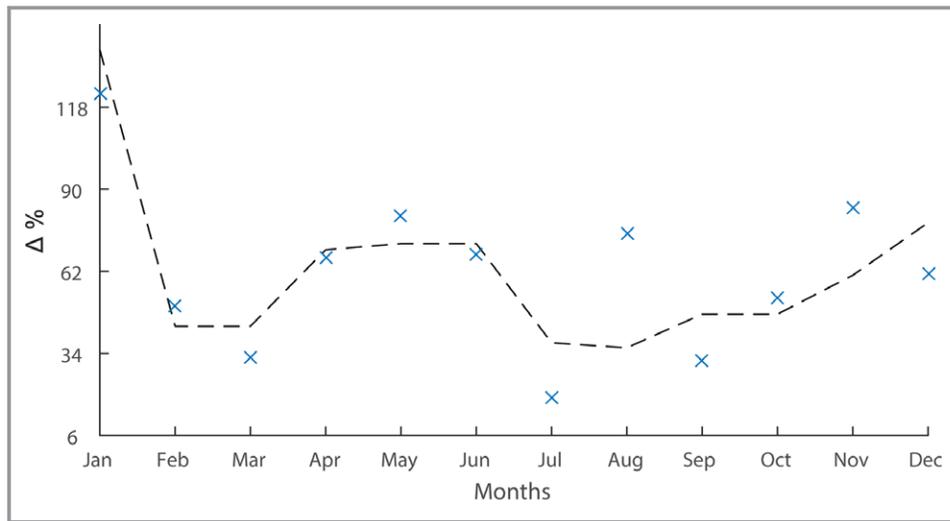
The arbitrary division of the day into intervals from 6:00 to 18:00 and from 18:00 to 6:00 is fixed, but in summer the real duration of the hours without light (real night) is decreased, and the wake-up time (when the peak of STEMI, if any, is observed) can be slightly anticipated, representing, more in theory than in practice, a minor but possible confounding factor. This could potentially generate a small bias that might contribute to an increase of STEMI during the 18:00-to-6:00 interval due to anticipation of the wake-up time. The need to nullify this confounding factor led us to study the pattern of STEMI at the equator, where the duration of light hours is nearly equal along the year, and seasons are not divided into winter, spring, summer, and autumn but are rather related with the monsoons and the onset of cloudiness that cover the sky and significantly reduce the sunshine. Furthermore, based on the above-mentioned findings, we suppose that the summer  $\Delta\%$  reduction could be related to the latitude of origin of the different populations, and this is true independently of the hemisphere of origin. In fact, the Australian population has well shown a remarkable  $\Delta\%$  reduction that in the Southern hemisphere occurs in a reverse trend (from December to March) with respect to the Northern hemisphere. Also for this reason, we decided to focus our attention

on the circadian behavior of STEMI across the year in Singapore, which is on the equator.

At the equator there is no standard seasonal partition as there is toward the polar zone, and, in contrast to the polar zone, the daylight duration is constant over the year. Hence, only at the equator could we detect the correlation of the  $\Delta\%$  variation with some important environmental and climatic factors, independently of the daylight duration changes (typical of the temperate climate zone) and the consequent bias. In order to answer this question we created a bimonthly bar plot (Figure 3A) that considers the  $\Delta\%$  variation in a population from Singapore. The bimonthly plot was preferred in order to reduce—in absence of large data numbers—the entropy caused by the higher sampling rate of monthly plot. We know that the average daylight hours are stable at the equator; thus, we computed the correlation between the  $\Delta\%$  bimonthly values and the bimonthly values of several climatic factors reported in Figure 3B. We were surprised to notice that the annual trend of the  $\Delta\%$  has a very strong negative correlation with the average *sunshine duration*. Whereas the daylight duration depends only on the sunrise and sunset times, the sunshine duration is an inverse indicator of cloudiness, and it is directly dependent on the level of irradiation. The sunshine duration is defined as the period during which direct solar irradiance exceeds a threshold value of  $120 \text{ W/m}^2$ .<sup>27</sup> Our data from Singapore suggest that the higher the sunshine duration, the more  $\Delta\%$  reduces, and, as a consequence, part of STEMI onsets significantly shift to the 18:00-to-6:00 (nocturnal) interval. Although the level of inverse correlation was very strong, this finding was so surprising for us that we believed it important to provide further validation. Thus, we considered 4 very heterogeneous and direct (not inverse like sunshine) cloudiness indicators



**Figure 4.** Correlation between the bimonthly  $\Delta\%$  signal (black line) in the overall Finnish cohort and the serum vitamin D bimonthly levels (red line) in a Swedish cohort of reference. The dashed line indicates the indicative threshold of 50  $\Delta\%$  for occurrence of summer shift effect.



**Figure 5.** Removal of noise and interpolation of the monthly  $\Delta\%$  signal in the overall Finnish cohort. Because the original monthly  $\Delta\%$  time series values (blue crosses) were noisy, we performed an advanced analysis and, in order to estimate a reduced-noise monthly  $\Delta\%$  time series signal, we applied a nonlinear adaptive filter—the median modified Wiener filter star—to the raw monthly  $\Delta\%$  for noise reduction and signal smoothing. The reduced-noise monthly  $\Delta\%$  time series signal is indicated by a dashed line and was used to compute the bimonthly time series signal displayed in Figure 4.

(Figure 3B). The results were that all 4 clouding indicators had a strong positive correlation with the trend of  $\Delta\%$ , and we speculate that the monsoon season might also play a role influencing the sunshine duration. The average temperature was the only indicator that in our analysis did not show any significant correlation with the trend of  $\Delta\%$  (Figure 3B). This is not a surprising result because the data from Singapore represented the basis for a null model in which effects related to daylight duration and temperature were minimized by hypothesis because they are negligible at the equator.

Again, although comforted by this confirmation, we needed more evidence to be convinced of this relation between the  $\Delta\%$  trend and sunshine variation. Accordingly, we considered other factors that relate to sunshine duration. Among the many molecules that are synthesized in the human body, the synthesis of vitamin D occurs in the keratinocytes present in the skin starting from cholesterol through a chemical reaction that is dependent on sun exposure (specifically UVB radiation). In fact, vitamin D is also known as the “sunshine” vitamin for its strong dependence on sunshine duration,<sup>28</sup> and for us it represented an appropriate molecular detector directly embedded within the human body to confirm the correlation between the  $\Delta\%$  trend and sunshine duration. Vitamin D produced in the skin is biologically inert and requires its hydroxylation to 25(OH)D in the liver. Therefore, 25(OH)D is the principal form of circulating vitamin D, and the levels of this metabolite best reflect the vitamin D status of an individual. In this regard, we considered the Finnish population because (1) it showed a trend that was not statistically significant, but there was still room to investigate its significance using a more refined

analysis; (2) we had available 2 different populations and hence the largest amount of samples. Therefore, we computed the bimonthly—which, we again stress, helped to reduce the entropy originated by the higher sample rate of the monthly interval— $\Delta\%$  signal for the overall (Finnish1+Finnish2=990 total individuals) Finnish population (Figure 4). And, in absence of Finnish data and without loss of generality (because Finland and Sweden are at the same latitude and there are no major climatic differences), we also plotted the average bimonthly vitamin D [more precisely the 25(OH)D serum levels] trend obtained from real data recently collected from a Swedish cohort.<sup>25</sup> Interestingly, although the Finnish cohorts showed only a trend in the previous analysis (Figure 2A), here the  $\Delta\%$  signal reached (at least in the July–August interval) a value lower than 50 that was the threshold previously suggested as a guideline for evidence of summer shift effect by the results in Figure 2B. Because vitamin D is dependent on the sunshine duration, this is further evidence that in the Finnish population as well, the  $\Delta\%$  trend seems inversely associated with the sunshine duration. Although this finding seems attractive, it needs to be tested more accurately using data from the same country, and we propose such investigations with the aims of raising interest and providing a starting point for the design of future studies.

## Discussion

Our findings are confirmed by the analysis of both prospective national studies and single-center registries. To the best of our knowledge, this is the first relevant evidence that

seasonal patterns might also significantly influence circadian variations in STEMI onset, in particular during the summer onset nadir. This summer shift of the occurrence of STEMI from the interval 6:00 to 18:00 to the interval 18:00 to 6:00 seems to be correlated (considering also the vitamin D seasonal fluctuations) with an important climatic indicator that is the sunshine duration. The sunshine duration influences vitamin D synthesis, is inversely associated with the level of cloudiness during the daylight hours, and should not be confused with the mere sunlight duration (which is simply the number of daylight hours). Both the evidence of the summer shift in the temperate climate zone and, in the absence of temperate seasons, the annual correlation of this shift with the sunshine duration at the equator, are important findings that can be of relevance for understanding the etiopathogenesis of STEMI onset. The prevalence of vitamin D deficiency in patients with acute myocardial infarction has been recently discovered, and its synthesis can affect many factors that participate in the etiogenesis of atherothrombotic coronary occlusion.<sup>29,30</sup> However, although in our epidemiological study we show that the summer shift correlates with the levels of vitamin D, this result should be taken with some caution. We stress that correlation does not imply causality, and, at the moment, no full molecular explanation of the mechanisms behind the summer shift is available.

A second remark is that nonclimatic factors induced by human intervention on the environment, such as the concentration of pollutants in the air,<sup>31</sup> can indirectly affect the sunshine duration and be confounding factors that should be considered in future investigations. We emphasize that important characteristics of the study populations are not known because the registries and studies we used were not built to specifically address to the relevant questions that emerged in our research. For instance, we do not know how many of the subjects were shift workers who are not exposed to typical sun exposure. Furthermore, we did not record diabetic status, renal function, which can affect the levels of vitamin D, and if any subjects were taking vitamin D supplements or other drugs that could potentially affect the results, such as  $\beta$ -blockers (populations of our study where these data were available accounted for <15%) and aspirin.<sup>32,33</sup> However, contrasting findings were reported regarding diabetic status and the absence of circadian rhythm, in particular the absence of an increased morning peak of STEMI incidence in diabetic patients.<sup>32-34</sup> Finally, in our study we address STEMI incidence but not outcome (eg, death), which might be another interesting variable to consider. However, it must be noted that outcome after a STEMI can be affected by several other confounding variables (in particular different health systems with different availability to primary coronary intervention) that could mask any effect of seasonal/circadian influence. In fact, in a study

performed in Minnesota, after multivariate adjustment for prehospital delay and door-to-balloon time, there was no significant association between circadian patterns of time of onset and in-hospital death.<sup>35</sup> Nevertheless, the issue regarding circadian rhythms, infarct size, and mortality remains a field of open discussion with contrasting reports, probably affected by origin of the study population and other variables.<sup>8,11,34,36</sup> Other important issues that need clarification are the genetic and ethnic background, which could influence circadian rhythms and seasonal patterns, even if this study found that the pattern of a summer shift can be observed in different ethnic and genetic backgrounds. Discovering molecular pathways associated with diseases plays a pivotal role in understanding the relation between cardiological pathologies and genetic factors.<sup>37</sup> We hope our findings will represent a convincing starting point for future studies to elucidate the molecular control factors and mechanisms behind these and even more complicated seasonal/circadian physiopathological phenomena, and we posit they could well have clinical implications on prognosis and treatment of cardiovascular disease.<sup>38</sup>

## Acknowledgments

Cannistraci thanks Ewa Aurelia Miendlarzewska, Eunhye Baek, and Alberto Cacciola for proofreading the article.

## Author Contributions

Cannistraci conceived the study. Cannistraci and Ammirati designed the study. Ammirati, Maseri, Cianflone, Nieminen, Viikilä, Laine, Nishi, Yeo, and Bhindi collected the data. Cannistraci designed the mathematical formulations and performed the computational analysis. Cannistraci envisioned the relation between summer shift and sunshine duration. Cannistraci created the figures and tables with suggestions from Ammirati. Cannistraci and Ammirati interpreted the results. Cannistraci wrote the article including major suggestions by Ammirati. All authors contributed to drafting the article and revised it critically so as to contribute to the interpretation. Cannistraci led, directed, and supervised the study. Ammirati, Maseri, Cianflone, Nieminen, Viikilä, Laine, Nishi, Yeo, and Bhindi—who were responsible for collecting the data—declare that all data were collected in accordance with the respective national regulations for the ethics approval and participants' consent.

## Sources of Funding

Cannistraci was supported by the independent group leader starting grant of the Technische Universität Dresden (TUD).

Cannistraci acknowledges support by the German Research Foundation and the Open Access Publication Funds of the Technische Universität Dresden.

## Disclosures

None.

## References

- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics—2016 update. *Circulation*. 2016;133:e38–e360.
- Libby P. Mechanisms of acute coronary syndromes. *N Engl J Med*. 2013;369:883–884.
- Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature*. 2011;473:317–325.
- Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E. Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med*. 1985;313:1315–1322.
- Toffler GH, Muller JE, Stone PH, Forman S, Solomon RE, Knatterud GL, Braunwald E. Modifiers of timing and possible triggers of acute myocardial infarction in the Thrombolysis in Myocardial Infarction Phase II (TIMI II) Study Group. *J Am Coll Cardiol*. 1992;20:1049–1055.
- Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol*. 1997;79:1512–1516.
- Edahiro R, Sakata Y, Nakatani D, Suna S, Usami M, Matsumoto S, Hara M, Kitamura T, Sato H, Yamashita S, Nanto S, Hikoso S, Sakata Y, Hori M, Hamasaki T, Komuro I; OACIS Investigators. Association of lifestyle-related factors with circadian onset patterns of acute myocardial infarction: a prospective observational study in Japan. *BMJ Open*. 2014;4:e005067.
- Ammirati E, Cristell N, Cianflone D, Vermi A-C, Marenzi G, De Metrio M, Uren NG, Hu D, Ravasi T, Maseri A, Cannistraci CV. Questing for circadian dependence in ST-segment-elevation acute myocardial infarction: a multicentric and multiethnic study. *Circ Res*. 2013;112:e110–e114.
- Jia E-Z, Xu Z-X, Cai H-Z, Guo C, Li L, Zhu T-B, Wang L-S, Cao K-J, Ma W-Z, Yang Z-J. Time distribution of the onset of chest pain in subjects with acute ST-elevation myocardial infarction: an eight-year, single-center study in China. *PLoS One*. 2012;7:e32478.
- Virag JAI, Lust RM. Circadian influences on myocardial infarction. *Front Physiol*. 2014;5:422.
- Ammirati E, Maseri A, Cannistraci CV. Still need for compelling evidence to support the circadian dependence of infarct size after ST-elevation myocardial infarction. *Circ Res*. 2013;113:e43–e44.
- Bochaton T, Ovize M. Circadian rhythm and ischaemia-reperfusion injury. *Lancet*. 2018;391:8–9.
- Stewart S, Keates AK, Redfern A, McMurray JJV. Seasonal variations in cardiovascular disease. *Nat Rev Cardiol*. 2017;14:654–664.
- Spencer FA, Goldberg RJ, Becker RC, Gore JM. Seasonal distribution of acute myocardial infarction in the second National Registry of Myocardial Infarction. *J Am Coll Cardiol*. 1998;31:1226–1233.
- Kriszbacher I, Bódis J, Boncz I, Koppan Á, Koppan M. The time of sunrise and the number of hours with daylight may influence the diurnal rhythm of acute heart attack mortality. *Int J Cardiol*. 2010;140:118–120.
- Spielberg C, Falkenhahn D, Willich SN, Wegscheider K, Völler H. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. *Am Heart J*. 1996;132:579–585.
- Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, Tomioka N, Okayama A, Nakamura Y, Ueshima H. Seasonal pattern of incidence and case fatality of acute myocardial infarction in a Japanese population (from the Takashima AMI Registry, 1988 to 2003). *Am J Cardiol*. 2008;102:1307–1311.
- Ornato JP, Peberdy MA, Chandra NC, Bush DE. Seasonal pattern of acute myocardial infarction in the National Registry of Myocardial Infarction. *J Am Coll Cardiol*. 1996;28:1684–1688.
- Enquesselassie F, Dobson AJ, Alexander HM, Steele PL. Seasons, temperature and coronary disease. *Int J Epidemiol*. 1993;22:632–636.
- Marchant B, Ranjadayalan K, Stevenson R, Wilkinson P, Timmis AD. Circadian and seasonal factors in the pathogenesis of acute myocardial infarction: the influence of environmental temperature. *Br Heart J*. 1993;69:385–387.
- Abrignani MG, Corrao S, Biondo GB, Renda N, Braschi A, Novo G, Di Girolamo A, Braschi GB, Novo S. Influence of climatic variables on acute myocardial infarction hospital admissions. *Int J Cardiol*. 2009;137:123–129.
- Cristell N, Cianflone D, Durante A, Ammirati E, Vanuzzo D, Banfi M, Calori G, Latib A, Crea F, Marenzi G, De Metrio M, Moretti L, Li H, Uren NG, Hu D, Maseri A; FAMI Study Investigators. High-sensitivity C-reactive protein is within normal levels at the very onset of first ST-segment elevation acute myocardial infarction in 41% of cases: a multiethnic case-control study. *J Am Coll Cardiol*. 2011;58:2654–2661.
- Helve S, Viikilä J, Laine M, Lilleberg J, Tieraal I, Nieminen T. Trends in treatment delays for patients with acute ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *BMC Cardiovasc Disord*. 2014;14:115.
- Ammirati E, Cannistraci CV, Cristell NA, Vecchio V, Palini AG, Tornvall P, Paganoni AM, Miendlarzewska EA, Sangalli LM, Monello A, Pernow J, Björnstedt Bennermo M, Marenzi G, Hu D, Uren NG, Cianflone D, Ravasi T, Manfredi AA, Maseri A. Identification and predictive value of interleukin-6<sup>+</sup> interleukin-10<sup>-</sup> and interleukin-6<sup>-</sup> interleukin-10<sup>+</sup> cytokine patterns in ST-elevation acute myocardial infarction. *Circ Res*. 2012;111:1336–1348.
- Klingberg E, Oleröd G, Konar J, Petzold M, Hammarsten O. Seasonal variations in serum 25-hydroxy vitamin D levels in a Swedish cohort. *Endocrine*. 2015;49:800–808.
- Cannistraci CV, Abbas A, Gao X. Median Modified Wiener Filter for nonlinear adaptive spatial denoising of protein NMR multidimensional spectra. *Sci Rep*. 2015;5:8017.
- W.M.O. *Guide to Meteorological Instruments and Methods of Observation*. 7th ed. World Meteorological Organization (WMO); 2008. Available at: <http://www.wmo.int>. Accessed March 26, 2018.
- Nair R, Maseeh A. Vitamin D: the “sunshine” vitamin. *J Pharmacol Pharmacother*. 2012;3:118–126.
- Aleksova A, Belfiore R, Carriere C, Kassem S, La Carrubba S, Barbati G, Sinagra G. Vitamin D deficiency in patients with acute myocardial infarction: an Italian single-center study. *Int J Vitam Nutr Res*. 2015;85:23–30.
- Lee JH, Gadi R, Spertus JA, Tang F, O’Keefe JH. Prevalence of vitamin D deficiency in patients with acute myocardial infarction. *Am J Cardiol*. 2011;107:1636–1638.
- Wang Y, Yang Y, Zhao N, Liu C, Wang Q. The magnitude of the effect of air pollution on sunshine hours in China. *J Geophys Res Atmos*. 2012;117:D00V14. DOI: 10.1029/2011JD016753.
- Kanth R, Ittaman S, Rezkalla S. Circadian patterns of ST elevation myocardial infarction in the new millennium. *Clin Med Res*. 2013;11:66–72.
- Sayer JW, Wilkinson P, Ranjadayalan K, Ray S, Marchant B, Timmis AD. Attenuation or absence of circadian and seasonal rhythms of acute myocardial infarction. *Heart*. 1997;77:325–329.
- Seneviratna A, Lim GH, Devi A, Carvalho LP, Chua T, Koh T-H, Tan H-C, Foo D, Tong K-L, Ong H-Y, Richards AM, Yew CK, Chan MY. Circadian dependence of infarct size and acute heart failure in ST elevation myocardial infarction. *PLoS One*. 2015;10:e0128526.
- Holmes DR, Aguirre FV, Aplin R, Lennon RJ, Nestler DM, Bell MR, Rihal CS, Ting HH. Circadian rhythms in patients with ST-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2010;3:382–389.
- Fournier S, Taffé P, Radovanovic D, Von Elm E, Morawiec B, Stauffer J-C, Erne P, Beggah A, Monney P, Pascale P, Iglesias J-F, Eeckhout E, Muller O. Myocardial infarct size and mortality depend on the time of day—a large multicenter study. *PLoS One*. 2015;10:e0119157.
- Cannistraci CV, Ogorevc J, Zorc M, Ravasi T, Dovc P, Kunjic T. Pivotal role of the muscle-contraction pathway in cryptorchidism and evidence for genomic connections with cardiomyopathy pathways in RASopathies. *BMC Med Genomics*. 2013;6:5. DOI: 10.1186/1755-8794-6-5.
- Nagy AD, Reddy AB. Time dictates: emerging clinical analyses of the impact of circadian rhythms on diagnosis, prognosis and treatment of disease. *Clin Med*. 2015;15(suppl 6):s50–s53.

## **"Summer Shift": A Potential Effect of Sunshine on the Time Onset of ST–Elevation Acute Myocardial Infarction**

Carlo Vittorio Cannistraci, Tuomo Nieminen, Masahiro Nishi, Levon M. Khachigian, Juho Viikilä, Mika Laine, Domenico Cianflone, Attilio Maseri, Khung Keong Yeo, Ravinay Bhindi and Enrico Ammirati

*J Am Heart Assoc.* 2018;7:e006878; originally published April 6, 2018;  
doi: 10.1161/JAHA.117.006878

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jaha.ahajournals.org/content/7/8/e006878>