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ABSTRACT & COMMENTARY

Public Health Interventions to Reduce COVID-19 Spread

By Seema Gupta, MD, MSPH

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Dr. Gupta reports no financial relationships relevant to this field of study.

SYNOPSIS: After studying the association of public health interventions with the epidemiological features of the COVID-19 outbreak in Wuhan, China, the authors found nonpharmaceutical interventions, including home confinement, social distancing, centralized quarantine, *cordons sanitaire*, and traffic restriction, may be associated with better outbreak control.

SOURCE: Pan A, et al. Association of public health interventions with the epidemiology of the COVID-19 outbreak in Wuhan, China. *JAMA* 2020; Apr 10. doi: 10.1001/jama.2020.6130. [Epub ahead of print].

Soon after its detection in Wuhan, China, coronavirus disease 2019 (COVID-19) evolved into a rapidly spreading infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Single-strand RNA viruses like this one can mutate quickly, adapt to different epidemiological situations, and infect many hosts (including avian, wild and domestic mammalian species, and humans).[1] SARS-CoV-2 can be transmitted between humans through aerosol droplets, direct contact, fecal-oral route, and intermediate objects from asymptomatic and symptomatic patients during the incubation period.[2] Symptoms may appear two to 14 days after virus exposure. Although primarily targeting the respiratory system, the disease is characterized by dry cough, fever, diarrhea, and dyspnea in 20% to 25% of patients who do not show upper respiratory signs, such as sore throat or sneezing.[3]

Currently, there is no vaccine available nor any pharmaceutical agents yet clearly identified to be safe and effective at preventing or treating COVID-19.[4] Therefore, there has been an undue reliance by the public health community on various nonpharmaceutical interventions (NPIs) to reduce the community-level spread of COVID-19. Such measures, such as social distancing, stay-at-home policies, travel restrictions, cancelation of schools and nonessential

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Internal Medicine
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businesses, and wearing cloth face masks, may work to mitigate and suppress new infections. NPIs could be an important tool in combating the global pandemic until a time when researchers can develop effective preventive and therapeutic countermeasures.

In their study, Pan et al evaluated the epidemiologic outcomes following implementation of NPIs during the COVID-19 outbreak in Wuhan, China, within weeks following the disease detection. They obtained individual-level data on 32,583 laboratory-confirmed COVID-19 cases and computed standardized number of infections per day per million people, effective reproduction numbers, and the proportion of severe disease in cases from December 2019 through early March 2020.

Interestingly, this time was calculated across five periods: Dec. 8 to Jan. 9 (no intervention), Jan. 10 to Jan. 22 (heavy population movement during Chinese New Year), Jan. 23 to Feb. 1 (city-wide lockdown with home quarantine, *cordons sanitaire*, and traffic restriction), Feb. 2 to Feb. 16 (centralized treatment and quarantine), and Feb. 17 to March 8 (door-to-door and individual-to-individual community screening survey of all residents).

Pan et al found that the local health workers had a higher daily confirmed case rate compared with that in the general population during the entire time period: 130.5 per million people (95% confidence interval [CI], 123.9-137.2) vs. 41.5 per million people (95% CI, 41.0-41.9). However, the proportion of critical and severe cases declined continuously from 53.1% to 10.3% over the five periods. The severity risk tended to increase with age. Finally, the daily confirmed case rate per million people increased from 2.0 before Jan. 10 to 45.9 between Jan. 10 and Jan. 22 and to 162.6 between Jan. 23 and Feb. 1. The rate then declined to 77.9 between Feb. 2 and Feb. 16, and to 17.2 after Feb. 16. Overall, Pan et al noted the series of multifaceted NPIs adopted was associated with improved better virus control in Wuhan.

■ COMMENTARY

The basic reproduction number (R_0) is the number of cases expected to occur on average in a homogeneous population when a single individual is infected, when everyone is susceptible at the start of the epidemic, before widespread immunity starts to develop, and before anyone attempts immunization.

However, R_0 cannot account for the time-varying nature of an epidemic. Thus, investigators may substitute a time-varying effective reproductive number (R_t) to provide more information because it tracks the subsequent evolution of transmission. If R_t is below 1, the epidemic eventually peters out. Above 1, it will grow — possibly exponentially.

In any communicable disease outbreak, it is critical to interrupt the chain of transmission by reducing the average number of cases caused by each infected individual over their infectious period, and bring the R_t to lower than 1. Pan et al provided an impressive account of the association between NPIs employed (especially travel restrictions and home quarantine) and lowering R_t to less than 1 in the early days of the Wuhan outbreak.

There are two main lessons to be learned from this study. First, we should sharpen our focus to better understand which NPI tactics produce the most return on investment when it comes to breaking the infectious cycle of the pandemic. Then, we should apply those methods as states and communities re-open across the nation.

The economic and social impact caused by widespread lockdowns are severe. A much more targeted approach may allow a successful control of the pandemic without recrudescence of infections. Second, we must enhance access to real-time data in the United States for those who are infected as well as those who need to undergo further testing, surveillance, and/or quarantine.[5]

There may be an extended period before a vaccine and/or effective pharmacotherapy is widely available. Evidence-based, focused NPIs, paired with a national, robust, real-time surveillance system, may just buy enough time to mitigate the current COVID-19 pandemic wave. ■

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BRIEF REPORT

Masking Our Anxiety

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Klompas M, et al. Universal masking in hospitals in the Covid-19 era. *N Engl J Med* 2020;382:e63.

Recently, while sitting in the intensive care unit, I noticed one of our renal specialists was adjusting her mask and complaining that it was uncomfortable to wear all day. I inquired why she was wearing it. She seemed puzzled, and responded, "Because of coronavirus." I had to tell her she was not really protecting herself, she was protecting me. She said, "Why am I wearing it?"

Experts are divided as to whether all healthcare workers (HCWs) — nay, everyone on the planet — should be wearing a mask. After a local academic center announced their universal mask policy last week, our facility felt arm-twisted into proceeding with similar guidance for our HCWs to mask in clinical areas. But when is it logical to initiate such a measure for HCWs? The pros and cons for this measure are as follows:

Pros

• Psychological benefit to the wearer. Right or wrong, people are psychologically more comfortable wearing a mask right now, allowing them to better focus on their jobs, even if they are physically more uncomfortable. Unfortunately, masks are a component of full personal protective equipment (PPE), including gowns, gloves, and face shields. By themselves, masks may provide only minimal protection to the wearer.

• Wearing a mask helps protect those around you. Data suggest a mask reduces the risk of potential transmission from an asymptomatic or minimally symptomatic HCW to fellow workers and patients. Notably, it is unclear to what degree such individuals may contribute to overall transmission.

• Reduced stigmatization for those wearing a mask who come to work with minimal or ambiguous symptoms. At least they feel more comfortable donning a mask if everyone else is.

Cons

• Masks are a valuable resource. Until sufficient masks are available for every HCW, every day, they should be conserved for more necessary duties.

• Is it rational (or even ethical) for me to wear a mask every day to work when colleagues in New York are at risk for running out of PPE? I do not feel comfortable with this.

• Masks are uncomfortable. Data suggest mask wearers touch their face and mask more often than those without a mask. Requiring employees to don a mask only in clinical areas guarantees they will be donning and doffing that mask all day, putting it down on a surface, or stuffing it in their pocket during lunch. Like clothing, I bet by the end of the shift that mask will be covered with various bacteria or viruses.

• If the goal is to reduce transmission to other employees, why is it recommended to remove the mask in nonclinical areas?

• On the other hand, if the goal is to reduce transmission to patients, then why are many hospital workers with limited or no contact with patients wearing a mask?

• Will it be practice or policy for HCWs to wear a mask in the healthcare environment? Is this one more thing a hospital is supposed to enforce? Just as there are some HCWs who desperately want to wear a mask, there are some who do not. Can you force them to wear a mask?

I do not see where personal comfort enters into this discussion. Good healthcare must be rational and based on sound principles, not fear. There must be some balance between the prevalence of disease in the population, the risk of transmission from asymptomatic individuals, and disease severity that leads to this decision. It feels like this decision is just masking our anxiety. ■

ABSTRACT & COMMENTARY

Coronary CT Angiography to Identify Plaque Stabilization

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study.

SYNOPSIS: Researchers identified subjects with no known coronary artery disease drawn from a large international, multicenter registry of coronary CT angiography. The authors demonstrated those with a high density of calcium plaques experienced the fewest events, suggesting high-density calcium plaques are stable.

SOURCE: van Rosendael AR, et al. Association of high-density calcified 1K plaque with risk of acute coronary syndrome. *JAMA Cardiol* 2020; Jan 22. doi: 10.1001/jamacardio.2019.5315. [Epub ahead of print].

Coronary artery plaque characteristics are believed to be important for assessing the likelihood of plaque rupture, based largely on pathology studies. Although the presence of coronary artery calcium on CT scans identifies plaques, more does not necessarily predict subsequent coronary events.

Van Rosendael et al sought to determine the relationship between increasing density of calcified plaque and the risk of an acute coronary syndrome (ACS). They developed a case-controlled, nested study called ICONIC. Using information from the CONFIRM registry, van Rosendael et al identified subjects with no known coronary artery disease (CAD), who had undergone coronary CT angiography (CCTA), and who had been followed for four years. Patients who experienced an ACS event were matched with those who did not, which resulted in 189 pairs. The density of coronary plaques was expressed in Hounsfield units (HU). Plaques were categorized as necrotic core, fibrofatty, fibrous, and calcified based on HU strata: < 30, 31-130, 131-350, and > 350, respectively. The authors focused on calcified plaques, and divided those into three groups: 351-700 HU, 701-1,000 HU, and > 1,000 HU. The latter group was termed 1K plaque. The mean age of the study population was 60 years, and 65% were men.

Total plaque volume was similar in the paired group. However, with each increasing calcium density stratum, calcium volume was lower in ACS subjects than in non-ACS subjects. The mean volume of 1K plaque in the ACS patients was 3.9 vs. 9.4 for the control subjects ($P = 0.02$). But for subjects > age 75 years, 1K plaque did not differ between patients and controls. Among the participants in the highest quartile of 1K plaque in both groups, there was more calcified plaque (48% vs. 25%; $P < 0.001$) and relatively less necrotic core plus fibrofatty plaque (13% vs. 25%; $P < 0.001$) compared to the other three quartiles. The authors concluded that on a per patient basis, the measure of high-density (> 1,000 HU), calcified plaque was associated with a lower risk of subsequent ACS.

■ COMMENTARY

The Multi-Ethnic Study of Atherosclerosis (MESA) study included subjects without known CAD. Those authors, using non-contrast, older generation CT scanners, showed that coronary artery calcium (CAC) volume and density were more predictive of the risk of CAD events than the pooled atherosclerosis risk score. The MESA authors used the Agatston score to assess calcium volume, which is upwardly weighted for more density of calcium. The authors estimated calcium density from the Agatston score, which was associated with fewer CAD events. Here, van Rosendael et al used newer multislice CT scanners. These machines provide higher HU values because of the effect of contrast, which attenuates vascular structures. These authors demonstrated that higher calcium density reduces the risk of CAD events. This suggests more calcium density equates to plaque stabilization. Thus, the best risk prediction would factor in calcium volume (more risk) and calcium density (less risk). Notably, a high calcium density (> 1,000 HU) showed a significant association with fewer ACS events. Lower values did not, demonstrating the equipoise for CAD events between calcium volume and density at lower densities. There were limitations to this study. The cohort was a subgroup derived from a larger registry study (CONFIRM), so there was selection bias and unmeasured confounders. In those > age 75 years, there was no association between calcium density and events, but this was a small group that was not as well matched. Also, subjects with total coronary artery occlusions were excluded, and the authors did not provide information on medication use. Thus, the study should be considered hypothesis-generating until a prospective, controlled study is completed. However, this study does support the results of MESA, extending the observations of those authors using newer CT scanners with contrast images of the coronary arteries. Van Rosendael et al believe the features of atherosclerotic plaques are important for estimating prognosis in those with CAD, and that a high density of calcium represents plaque stability. Pathogenic studies have supported this concept because they have shown that ruptured plaques tend to be fibroatheromas

with large necrotic cores and thin, inflamed fibrosis caps. The noninvasive detection of vulnerable plaques is the Holy Grail of coronary imaging. How does this study of presumably stable high-density calcium plaques help clinicians? Based on the results of other studies, statins increase calcium volume and reduce the volume of the necrotic core in plaques. Presumably, many of the stable patients in the van Rosendael et al study were on statins. If not, would adding a statin to all those with calcium densities < 1,000 HU (but not to those > 1,000 HU) make sense? The former might, but I am not sure about the latter. This study adds support to the plaque stabilization by calcium theory and highlights the lack of value of serial CCTA imaging at this point in technologic development. Also, it emphasizes that the industry has moved on from the Agatston score and the need to use the advanced quantitative features of current CCTA imaging. ■

BRIEF REPORT

Brief, Targeted Intervention to Stop Smoking

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: A one-minute intervention giving facts about the health impact of smoking was presented to 787 men waiting to be seen in Hong Kong emergency rooms. At a six-month follow-up, investigators found a significantly higher abstinence rate in the intervention group.

SOURCE: Li HCW, et al. Effectiveness of a brief, self-determination intervention for smoking cessation (immediate or progressive) among people attending emergency departments: A randomised controlled trial. *Tobacco Induced Diseases* 2018;16:870. doi:10.18332/tid/84430.

In the time of COVID-19, it seems difficult to focus on any other public health problem. Yet, smoking and tobacco use continue to represent major health morbidity and mortality risks worldwide, causing more than 7 million deaths each year.[1] Li et al noted that previous research indicates many patients are not fully motivated to quit smoking, but that many smokers report a desire to reduce the number of cigarettes smoked. The group postulated an intervention following the principles of self-determination theory would be useful in motivating tobacco abstinence. Specifically, this decision-making framework encourages development of intrinsic motivation, autonomy, and personal responsibility.[2] When applied to the problem of tobacco use, self-determination theory allows patients more personal decision-making and responsibility in arriving at a smoking cessation timeline and designing a "quit" program.

To test this theory, Li et al engaged healthcare professionals to recruit smokers who presented to four different Hong Kong emergency departments (EDs). Eligible adults were randomized to either an intervention or a control group. The control group received a smoking cessation pamphlet. The intervention group was given brief, direct advice following the AWARD model: Ask (about smoking history), Warn (about dangers), Advise (to quit), Refer (to smoking cessation hotline), and Do again.[3] Of the 4,228 eligible smokers approached, 1,517 agreed to participate. Follow-up occurred at one, three, six, and 12 months with biochemical validation of smoking status at six months as the primary outcome. Other outcomes included biochemical validation of smoking status at month 12 and self-reported reduction in tobacco use by at least 50% at months 6 and 12.

In total, 787 persons were randomized to the intervention group and 784 to the control group. In the intervention group, 6.7% had biochemical validation of abstinence from tobacco at six months, while only 2.8% of those in the control group had the same. This was a statistically significant difference. However, when looking at self-reported reduction in tobacco use between the two groups, no statistically significant difference is noted. At the 12-month follow-up, results remained fairly consistent with results from the six-month mark. The results from this study imply that a brief intervention delivered to a "captive" audience (patients waiting at an ED) may be effective in motivating some individuals to stop smoking. It is notable that about 64% of eligible patients declined to be part of the study; the 35.9% who did agree to participate may represent a group with some bias toward smoking cessation. However, as the full group of participants was randomized, this bias should not influence results. Perhaps "less is more," and the length of time spent in an intervention may be unrelated to outcomes.

It is interesting to speculate that some of the relative success of this intervention may be related to delivering the message while patients were waiting in an ED. Although patients with life-threatening, acute illnesses were not eligible for the study, visiting an ED even for a less urgent reason may raise a person's awareness of personal vulnerability and increase motivation for adopting healthier habits. It is difficult to know what to make of the nonsignificant findings regarding reduction in tobacco use by more than 50%. In the future, researchers may want to understand this aspect in more depth and develop a method of external validation. Li et

al stated the relative success of the intervention is based on delivering a brief, factual message and then offering patients autonomy regarding action and follow-up. This follows the self-determination theory, a decision-making and motivation model. Follow-up studies are needed to determine generalizability. Still, in the interim, this quick intervention and the underlying principle is suitable for front-line clinician implementation. Considering that stopping smoking may be helpful in mitigating the course of an upper respiratory infection associated with the coronavirus, this message may carry even more relevance for the immediate future. ■

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PHARMACOLOGY UPDATE

Remdesivir Injection

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for remdesivir to treat patients who are severely ill with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), often referred to as COVID-19.[1] Remdesivir is a prodrug that is metabolized intracellularly to an analog of adenosine triphosphate, acting as an inhibitor of RNA-dependent RNA polymerase.[1] It has shown activity in animal models against two other coronaviruses (SARS-CoV-1 and MERS-CoV), in vitro activity against SARS-CoV-2, and possible evidence of benefit during compassionate use.[2,3] Remdesivir is manufactured by Gilead Sciences.

INDICATIONS

Remdesivir can be used to treat suspected or laboratory-confirmed COVID-19 in children or adults who are hospitalized with severe disease. Severe disease is defined as oxygen saturation ≤ 94% on room air or requiring supplemental oxygen, extracorporeal membrane oxygenation (ECMO), or mechanical ventilation.[4]

DOSAGE

The recommended dose for patients weighing ≥ 40 kg requiring invasive mechanical ventilation and/or ECMO is 200 mg infused intravenously over 30 to 120 minutes on day 1 and 100 mg once daily for nine days.[4] For patients between 3.5 kg and < 40 kg, the dose is 5 mg/kg on day 1 and 2.5 mg/kg once daily up to 10 days. Remdesivir is available as a 100-mg vial.

POTENTIAL ADVANTAGES

The FDA deemed that the known and potential benefits of remdesivir outweigh the known and potential risks for the treatment of hospitalized patients with COVID-19.[1] Currently, there are no adequate, approved, alternative therapies to remdesivir.

POTENTIAL DISADVANTAGES

The benefit of remdesivir appears to be modest, and survival benefit has not been established. Common adverse events included nausea, acute respiratory failure, and elevated liver enzymes.[5]

COMMENTS

The EUA for remdesivir was based on an interim analysis of the ongoing National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Adaptive COVID-19 Treatment Trial (ACTT, NCT04280705).[5] The study included hospitalized subjects with advanced COVID-19 and lung involvement. Subjects were randomized to remdesivir (n = 286) or placebo (n = 286). The primary outcome measure was time to recovery. This was defined as: hospitalized, not requiring supplement oxygen-no longer requiring ongoing medical care; not hospitalized, limitation on activities, and/or requiring home oxygen; not hospitalized, no limitation on activities. The remdesivir group recovered 31% faster, a median of 11 days vs. 15 days for the placebo group ($P < 0.001$). Numerically, survival benefit favored remdesivir (8% vs. 11.6%) but did not reach statistical significance ($P = 0.059$).

Recently, Gilead Sciences announced results from an open-label, Phase III trial that demonstrated similar efficacy with five- and 10-day dosing duration (median of 10 days vs. 11 days).[6] The authors of a small study out of Wuhan, China (n = 236) that did not reach target enrollment found no difference between remdesivir (n = 158) and placebo (n = 78) in clinical benefit in terms of time to clinical benefit and time to virus clearance.[7] However, those who received remdesivir within 10 days of symptom onset recorded a numerically faster (but not statistically significant) time to clinical improvement (median 18 days vs. 23 days). Limitations of this study included lack

of statistical power and initiation of treatment later in the disease course because of logistics (hospital bed availability).

CLINICAL IMPLICATIONS

As of this writing, there are no curative or FDA-approved therapies for COVID-19 (i.e., deemed to be safe and effective). Remdesivir appears to offer modest benefit and is the first antiviral authorized for emergency use. NIAID decided to terminate ACTT as originally designed, forgoing the opportunity to assess whether there is a definitive survival advantage for remdesivir.[8] ACTT2 is evolving to a two-arm study comprised of remdesivir plus an anti-inflammatory agent, baricitinib, compared to remdesivir plus a placebo.[9] Baricitinib is a Janus kinase inhibitor that has been approved for treating rheumatoid arthritis. A study of remdesivir in moderate COVID-19 is in process, with results expected soon. Although remdesivir requires a difficult, multistep manufacturing process, Gilead is committed to donating 1.5 million doses of remdesivir. The company is expected to start charging for the drug in July.[10] ■

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CME QUESTIONS

1. Based on the results of the study by Pan et al, which statement is true?
a. Local health workers had a lower daily confirmed case rate from COVID-19 compared with that in the general population.
b. The proportion of severe and critical cases first increased and then decreased over the five periods.
c. The severity risk tended to increase regardless of age.
d. The daily confirmed case rate per million people first increased and then decreased over the five periods.

2. From a registry of subjects without known coronary artery disease who underwent a CT coronary angiogram, those with subsequent acute coronary syndromes were compared to those without. The former showed:
a. more plaque volume.
b. lower plaque density.
c. less fibro-fatty plaque.
d. less necrotic core.

3. Which is true regarding smoking cessation and a one-minute intervention?
a. More than 50% of the intervention group demonstrated biochemical validation of abstinence from tobacco use at the six-month and 12-month marks, about twice the level of the control group.
b. Between 6% and 7% of the intervention group demonstrated biochemical validation of abstinence from tobacco use at the six-month and 12-month marks, about twice the level of the control group.
c. Although there were no significant differences in biochemical validation of abstinence from tobacco, the intervention group showed clear patterns of a steady reduction in cigarettes smoked.
d. There were significant differences between the intervention and control groups in both abstinence and in reduction of cigarettes by > 50%.

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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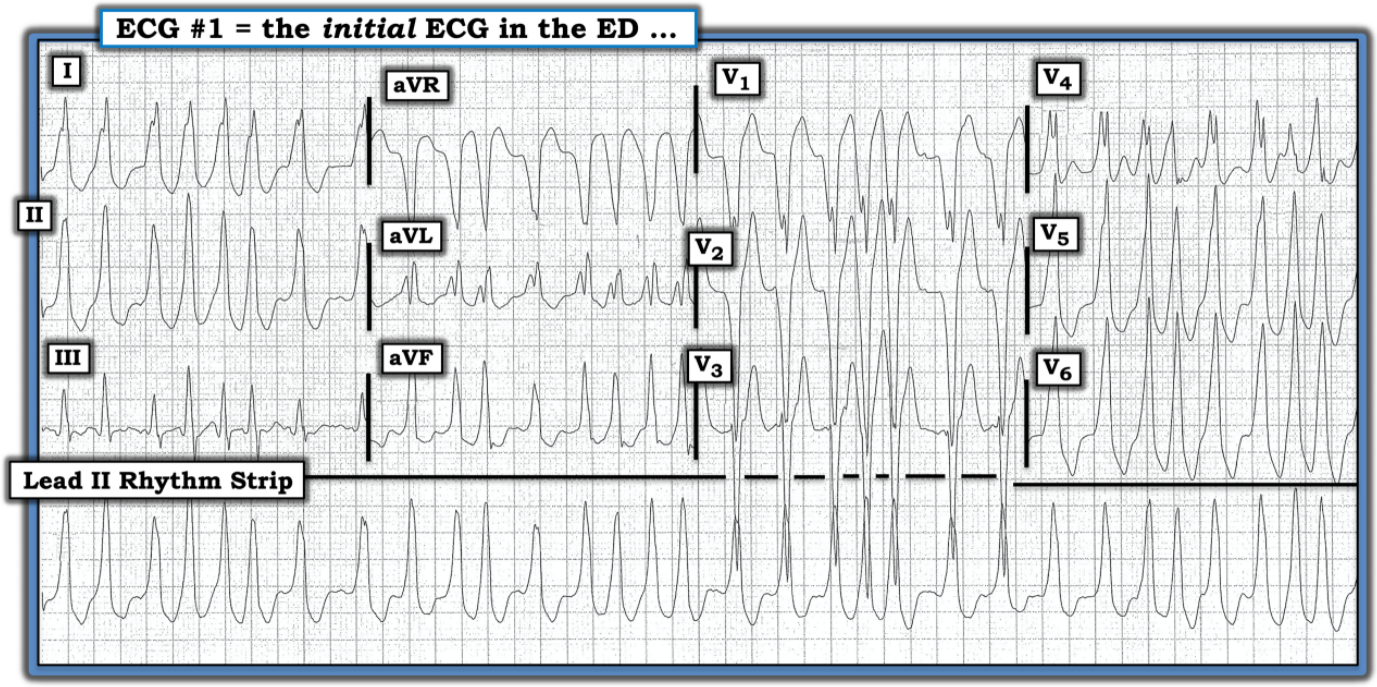
Dr. Grauer reports no financial relationships relevant to this field of study.

How Can This Patient Be Stable?

The ECG in the figure below was obtained from a young adult who presented to the emergency department with palpitations, but who otherwise was hemodynamically stable. What is the diagnosis?



The rhythm in this ECG is rapid and irregularly irregular. The QRS complex is obviously wide. P waves are absent. Therefore, this rhythm qualifies as an irregular wide complex tachycardia rhythm. The finding of an irregularly irregular tachycardia without clear sign of P waves on any of the 12 leads suggests the rhythm to be atrial fibrillation (AF).

The key to interpretation of this tracing lies with determination of the heart rate. Note the R-R interval for more than a few of the complexes in the long lead II rhythm strip is barely the length of one large box long. This corresponds to a ventricular rate that at times exceeds 220 (if not 250) beats per minute.

Normally with AF, the AV node refractory period limits the number of fibrillation impulses that can be conducted to the ventricles to less than 200 beats per minute. The fact that the ventricular response is at times much faster than this indicates that AF impulses cannot be conducting over the normal AV nodal pathway. Instead, fibrillation impulses must be conducting over an accessory pathway. This tells us that the patient must have Wolff-Parkinson-White (WPW) syndrome. Several additional features support the conclusion that this patient has WPW. There is marked variation in the duration of R-R intervals on this tracing. There is variation in QRS morphology. Both of these ECG findings are in contrast to what happens with monomorphic ventricular tachycardia (VT), in which the rhythm will not be this irregular, and will not manifest this degree of variation in QRS morphology. Finally, a characteristic feature seen in younger adults with WPW, who otherwise do not have underlying heart disease, is that they often remain hemodynamically stable for surprisingly long periods, despite attaining heart rates as rapid as we see in this figure. Patients with VT are far less likely to remain hemodynamically stable for a sustained period with heart rates that exceed 220 beats per minute.

For more information about and further discussion on this case, please visit: https://bit.ly/2Lu4JZ6.