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Internal Medicine

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ABSTRACT & COMMENTARY

Two Possible Mechanisms of Disease in COVID-19

By Neal S. Parikh, MD, MS

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Dr. Parikh reports no financial relationships related to this field of study.

SYNOPSIS: COVID-19 infection may be associated with an increased risk of blood clotting and related thrombotic events, but there are insufficient data to support indiscriminately discontinuing medications that play a critical role in the management of chronic cardiovascular disease.

SOURCES: Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020;382:e38.

Mehra MR, Desai SS, Kuy S, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med* 2020; May 1. doi: 10.1056/NEJMoa2007621. [Online ahead of print].

COVID-19 infection has taken the world by storm. The first few months of the pandemic have been met by a powerful demonstration of insightful clinical investigation. Clinicians quickly noticed patients with COVID-19 infection appear to face an increased risk of cardiovascular events and high rates of mortality. Researchers are striving to understand precisely why this is the case.

Even before clinicians had accrued sufficient COVID-19 patient care experience, investigators were aware of the virus's biology. Early in the pandemic, it was known COVID-19 gains entry into the human body by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. ACE1 is the site of action of a commonly used drug class, namely ACE inhibitors. ACE1 and ACE2 are involved in a complex feedback loop. On this basis, investigators hypothesized that the use of ACE inhibitors, and the related drug class of angiotensin receptor blockers (ARBs), may increase the expression of ACE2, thereby increasing the entry of COVID-19 into the lungs. This gave rise to the concern that using ACE inhibitors and ARBs may increase the severity of COVID-19. At the population

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level, indiscriminate cessation of these drugs would lead to uncontrolled hypertension, heart failure, and other unintended consequences. Thus, understanding whether these commonly used drugs truly contribute to mortality in COVID-19 demanded investigation.

Mehra et al sought to address this critical question. In a remarkable feat, considering the short period between the first case of COVID-19 and the publication of their manuscript, the authors performed a large, multicenter, observational study using data from 169 hospitals. They tabulated patients' demographics and comorbidities in addition to their medication history. Then, they performed multivariable regression analyses to evaluate whether the use of ACE inhibitors or ARBs was associated with an independently higher risk of in-hospital mortality. Of 8,910 hospitalized patients, 515 died in the hospital. Patients who died were older and had a higher burden of coexisting conditions, such as heart disease, diabetes, and pulmonary disease.

In their statistical models, older age and heart disease were independently associated with in-hospital mortality, but use of ACE inhibitors and ARBs was not. In fact, ACE inhibitors may have been protective. The authors appropriately noted they made many statistical comparisons, and their data are retrospective, so it is not justified to conclude ACE inhibitors are truly protective. However, their data do allay concerns about the safety of these medications in COVID-19.

As clinicians see more cases of COVID-19, they begin to accumulate observations that inform additional hypotheses to explain why this virus dramatically increases the risk of thrombotic events and death. Doctors caring for patients with COVID-19 began to notice a high rate of blood clotting in their patients. To explain this, they investigated whether COVID-19 infection results in antiphospholipid antibody production, which is characteristic of its namesake, sometimes-catastrophic, blood clotting disorder. Provocatively, Zhang et al reported three cases of patients with COVID-19 with positive antibodies. Whether COVID-19 induces a prothrombotic state, and the optimal management of this condition, requires further work.

■ COMMENTARY

COVID-19 clinical investigation sets the bar for clinical research. Physicians and investigators have promptly identified and answered critical questions with robust methods, without neglecting pathophysiology or underestimating the value of empiric clinical observation. Taken together, all these data demonstrate COVID-19 is associated with a high rate of in-hospital mortality, but that ACE inhibitors and ARBs likely should not be discontinued, and certainly not in the population at large.

Meanwhile, there are emerging data showing that COVID-19 may, as is the case with other infections, result in a prothrombotic state linked to the generation of antiphospholipid antibodies. If confirmed, future work surely will investigate antithrombotic regimens and perhaps therapies to quell the production of these antibodies. Apart from prevention and mitigation of infection, therapies to prevent complications of COVID-19 are needed urgently. ■

ABSTRACT & COMMENTARY

Early Data on Remdesivir for Severe COVID-19: A Promising Start?

By Betty Tran, MD, MSc

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

SYNOPSIS: In this group of patients hospitalized with severe COVID-19, most of whom required invasive ventilation, 68% showed clinical improvement after treatment with remdesivir on a compassionate-use basis.

SOURCE: Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med* 2020; April 10. doi: 10.1056/NEJMoa2007016. [Online ahead of print].

COVID-19 has overwhelmed health systems globally, with more than 9.2 million confirmed cases and more than 478,000 deaths as of this writing.[1] In severe cases requiring admission to the intensive care unit (ICU) or invasive ventilation, mortality rates upward of 60% to 70% have been reported.[2-3] Currently, there is no proven effective therapy, and management has largely consisted of supportive care, including various forms of oxygen support. Trials using antiretrovirals, anti-inflammatory agents, and convalescent plasma are ongoing.

Remdesivir is a prodrug of a nucleotide analogue that inhibits viral ribonucleic acid (RNA) polymerases. The manufacturer sponsored early compassionate use of remdesivir for hospitalized COVID-19 patients beginning Jan. 25, 2020. Criteria included oxygen saturation 94% or lower while breathing room air or on oxygen support, a creatinine clearance above 30 mL/minute, serum transaminases less than five times the upper limit of normal, and patients taking no other investigational agents for COVID-19. Planned treatment consisted of a 10-day course of remdesivir, with a loading dose of 200 mg intravenously (IV) on day 1, followed by 100 mg daily for nine days. Follow-up was continued through at least 28 days after beginning treatment or until discharge or death.

In total, 61 patients received at least one dose of remdesivir, although eight patients were excluded because of missing baseline information or an erroneous start date, leaving 53 patients for analysis. Seventy-five percent of these received the full 10-day treatment. Patients from the United States, Europe, and Canada comprised the bulk of the cohort. The median age was 64 years (interquartile range [IQR], 48-71), 75% were male, and at baseline 34 patients received invasive ventilation (30 on mechanical ventilation, and four received extracorporeal membrane oxygenation [ECMO]). The median duration of symptoms before initiation of remdesivir treatment was 12 days (IQR, 9-15).

Over a median of 18 days (IQR, 13-23) after receiving remdesivir, 36 of 53 patients improved regarding oxygen support, including 17 of 30 patients receiving invasive mechanical ventilation who were extubated and three of four patients on ECMO who stopped receiving it. As of the last follow-up, 25 of 53 patients had been discharged (24% of those who received invasive ventilation, 89% of those receiving noninvasive ventilation support). Overall mortality in the cohort was 13%. Adverse events, most commonly increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension, occurred in 60% of patients, with 23% of patients experiencing serious adverse events (e.g., multiple organ dysfunction, septic shock).

■ COMMENTARY

This preliminary report describing the clinical outcomes seen in a small group of patients hospitalized for severe COVID-19 disease treated with remdesivir is encouraging, although interpretation is difficult, primarily given the lack of a randomized control group. Remdesivir produces broad-spectrum activity against a variety of virus families, produces in vitro activity against SARS-CoV-2, and has shown a favorable safety profile. It is unclear whether the listed adverse events from this report were a result of remdesivir, since these issues have been reported as part of the disease spectrum of COVID-19.

After this report was published, a randomized, double-blind, placebo-controlled multicenter trial out of Hubei, China, revealed no statistically significant benefits for remdesivir, although there was a trend toward faster time to clinical improvement among those who received it.[4] However, a few points are noteworthy. First, patients enrolled in this study were allowed to receive lopinavir-ritonavir, steroids, and interferons concomitantly. Second, the study authors stopped enrolling early, with a subsequent reduction in statistical power from 80% to 58%. Third, the patient population in the Hubei study included fewer patients on higher oxygen support (i.e., high-flow nasal cannula, noninvasive or invasive mechanical ventilation, ECMO): 18% of the remdesivir group, 13% of the placebo group.

In contrast, recently, a preliminary analysis of a National Institute of Allergy and Infectious Diseases clinical trial revealed COVID-19 patients treated with remdesivir recovered 31% faster vs. placebo patients ($P < 0.001$), with a median time to recovery of 11 vs. 15 days.5 Furthermore, a survival benefit was suggested, with a mortality rate of 8% for the remdesivir group vs. 11.6% for the placebo group ($P = 0.059$).[5] Also important: Regardless of these mixed findings, remdesivir has not been shown to be curative or preventive. As we await more formal details from these trial results, we should continue the type of ICU-level care that has resulted in clinically meaningful outcomes for critically ill patients after decades of research, namely the A2F bundle (Assessing/preventing/managing pain, both spontaneous awakening and breathing trials, choice of analgesia/sedation, delirium assessment/prevention/management, early mobility/exercise, and family engagement).[6] ■

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ABSTRACT & COMMENTARY

MUCH Ado About WUCH

By Michael H. Crawford, MD

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

SYNOPSIS: In a long-term, fixed-drug therapy of hypertension study, masked uncontrolled and white coat uncontrolled hypertension exhibited poor reproducibility over four years.

SOURCE: Mancia G, Facchetti R, Cuspidi C, et al. Limited reproducibility of MUCH and WUCH: Evidence from the ELSA study. *Eur Heart J* 2020;41:1565-1571.

Recent outcome studies of hypertension management have focused on masked uncontrolled hypertension (MUCH), where only office blood pressure (BP) is controlled (not home BP), and white coat uncontrolled hypertension (WUCH), where only home BP is controlled. In some studies, both have shown an increase in cardiovascular outcomes. The authors of these studies almost always only measured ambulatory BP once. Thus, the long-term reproducibility of MUCH and WUCH is unclear.

Accordingly, Mancia et al interrogated the European Lacidipine Study on Atherosclerosis (ELSA), a comparison of the effect of a calcium channel blocker to a beta-blocker on carotid intima-media thickness (CIMT) over an average of four years. The authors examined the annual assessments of office and ambulatory BP measurements for the stability of MUCH and WUCH. Only patients with at least two annual measurements were included, resulting in 1,664 subjects studied. At baseline, the prevalence of patients with white coat hypertension was 13%. After one year of treatment, the prevalence of MUCH was 18%, WUCH 21%, and controlled hypertension 45%.

These relative prevalences remained constant throughout the four-year study, but there were large shifts of patients from one category to another. Only 34% to 41% of MUCH patients maintained this classification one or more years later, while 38% to 45% of WUCH patients maintained this classification. Controlled hypertension (office and ambulatory) was more consistent (46% to 57% persistence), as was uncontrolled hypertension (61% to 68%). The most common category shift for MUCH patients was to uncontrolled hypertension. Few patients among 918 with complete datasets with MUCH or WUCH maintained these classifications throughout (5% and 6%, respectively). These properties did not vary with the type of randomized treatment. The authors concluded that both MUCH and WUCH exhibit poor reproducibility over time on a constant drug regimen. This calls into question the prognostic value of these classifications if measured only once.

■ COMMENTARY

The original definition of masked and white coat hypertension came from observations in untreated patients. Outcome studies demonstrated that white coat hypertension was associated with persistent hypertension later in life. However, long-term outcomes are unclear, as is whether white coat hypertension needs to be treated pharmacologically. Masked hypertension has been associated with a higher risk of sustained hypertension, diabetes, and organ damage, which is almost as high as sustained hypertension. Masked hypertension is common. The incidence in the Hypertension Optimal Treatment (HOT) study was 25%; in the Spanish hypertension registry, it was 30%. Mancia et al recorded a rate of 18%. Also, masked hypertension has been reported in up to 16% of presumably healthy individuals, especially young people with borderline office blood pressures.

However, the effect of pharmacologic treatment of isolated masked hypertension is unclear. The Mancia

et al study took these concepts into a pharmacologic hypertension treatment trial, which concerned the comparative effects of two classes of drugs on atherosclerosis measured by CIMT. The patients were put on fixed doses of lacidipine or atenolol for four years without regard for BP control after the initial titration phase to a diastolic BP < 95 mmHg. This created an opportunity to study the reproducibility of MUCH and WUCH independent of drug therapy. Mancia et al demonstrated poor reproducibility of both, which was independent of the drug therapy. Patients with completely controlled or completely uncontrolled hypertension demonstrated significantly better reproducibility.

Other shorter studies with measurements in two-month intervals have shown better reproducibility of these four subgroups. Hypertension is a long game, so clinicians need long-term reproducibility to assess outcomes. In MUCH patients, the most common category change was to completely uncontrolled.

Considering the poor outcomes reported in other studies, it would seem that MUCH should be treated. It is less clear what to do with WUCH. One of the strengths of the Mancia et al study was the use of standardized office and high-quality ambulatory BP measurements rather than home BP. However, other studies have shown the variability in ambulatory BP measurements is high. Weaknesses of this study included the lack of data on drug adherence and annual measurements of BP rather than more frequent assessments. Also, the authors reported no outcome data, probably because there were few events in ELSA. Pending future research, it seems patients who report high home BPs (but who record normal office BP) would be ideal candidates for ambulatory BP studies during therapy. ■

BRIEF REPORT

Cloth Masks — Just for Looks?

By Carol A. Kemper, MD, FACP

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

SOURCE: MacIntyre CR, Seale H, Dung TC, et al. A cluster randomised trial of cloth masks compared with medical masks in healthcare workers. *BMJ Open* 2015;5:e006577.

How effective are homemade fabric masks many are using to protect others from COVID-19 transmission?

MacIntyre et al conducted a randomized clinical trial that evaluated the effectiveness of cloth vs. regular procedural masks in 1,607 healthcare workers (HCWs), recruited for study at 14 different hospitals in Hanoi, Vietnam, in 2011. The HCWs worked full-time in 74 high-risk units of the hospital, including the emergency departments, intensive care units, and infectious disease units. The HCWs were randomized to wear a regular procedural mask, cloth mask, or no mask throughout an eight-hour shift for four weeks. Then, they were followed for an additional one week for signs of respiratory illness.

Either two procedural masks were provided to each worker per shift, or five cloth masks were provided per month, which were to be washed and rotated throughout the four-week study period. HCWs also were asked to wear their masks throughout their shifts, except for tea, meal, and bathroom breaks. Each HCW maintained a diary of the number of patient contacts per shift and their activities, including suctioning, sputum induction, intubation, and bronchoscopy. At the first onset of symptoms, HCWs reported for evaluation and respiratory polymerase chain reaction (PCR) panel testing. HCWs logged an average of 36 patient contacts per day. Those with cloth masks reported they washed their masks 23 of 25 days, either at home (80%), using the hospital laundry (4%), or both (16%).

Despite the fact that workers reported better compliance with cloth masks, an intent to treat analysis showed rates of clinical respiratory illness, influenza-like illness (ILI), and laboratory-confirmed respiratory infection were significantly higher in the cloth mask group vs. the procedural mask group. Laboratory confirmation of respiratory viral infection was detected in 31 of 659 cloth mask users vs. 19 of 580 medical mask users. The relative risk of ILI in the cloth mask group, compared with the other groups, was 13.25. Surprisingly, no significant difference was observed in the rates of infection between those wearing medical masks and those without masks. The reported frequency of hand washing was found to be significantly protective against clinical respiratory illness.

In the laboratory, the penetration of particles through cloth masks was significantly higher (97%) than with either medical masks (44%) or N95s (< 0.01%). In addition to barrier protection, it is conceivable other factors may be responsible for this observed difference in the

risk of respiratory illness. Workers may re-adjust cloth masks more often than medical masks. Certain types of cloth used for such masks may be better at "acquiring" viral particles as workers move through their day, or the warm moisture from breathing may allow improved virus survival on masks. ■

PHARMACOLOGY UPDATE

Elagolix, Estradiol, and Norethindrone Acetate Capsules (Oriahnn)

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 approved the first oral treatment for heavy menstrual bleeding caused by uterine fibroids. This combination product contains elagolix (a nonpeptide gonadotropin-releasing hormone antagonist), estradiol, and a progestin, norethindrone acetate. Estrogen is added to attenuate the hypoestrogenic effects (e.g., decreased bone mineral density, hot flushes) of elagolix. Norethindrone acetate is added to protect the uterus from unopposed estrogen. Elagolix was approved in 2018 for the management of moderate to severe pain associated with endometriosis. Elagolix, estrogen, and norethindrone acetate (elagolix-EN) is marketed as Oriahnn.

INDICATIONS

Elagolix-EN should be prescribed to manage heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.[1]

DOSAGE

The recommended dose is one capsule in the morning and one in the evening, starting within seven days from the onset of menses.[1] The morning capsule contains elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg. The evening capsule contains elagolix 300 mg. The use of elagolix-EN should be limited to 24 months because of potential irreversible continued bone loss.[1] Elagolix is available as weekly blister packs, with seven morning capsules and seven evening capsules.

POTENTIAL ADVANTAGES

Elagolix-EN is the first FDA-approved, non-surgical treatment specifically for this indication.[2]

POTENTIAL DISADVANTAGES

Estrogen and progestin combinations increase the risk of thrombotic or thromboembolic disorders and are contraindicated in women with current, a history of, or at increased risk for these events.[1] This includes smokers, women with uncontrolled hypertension, and women older than age 35 years. Elagolix-EN also is contraindicated in pregnancy, osteoporosis, current or history of breast cancer, known hepatic impairment or disease, or concomitant use of organic anion transporting polypeptide inhibitors.[1] Increases in total cholesterol, low-density lipoprotein, triglycerides, and apolipoprotein can occur with greater changes in those with higher baseline levels.[1] Depression and related symptoms were reported in 3% of elagolix-EN-treated subjects vs. 1% in placebo-treated subjects. Fractures were observed in 1.5% of elagolix-EN-treated subjects vs. 0.5% for the placebo group.[1] Seventy-one percent of fractures occurred in the post-treatment follow-up period. The most common adverse reaction is hot flush (22% vs. 9% for placebo). Elagolix-EN contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in certain susceptible patients (e.g., those with aspirin hypersensitivity).[1]

COMMENTS

The efficacy of elagolix-EN was assessed in two randomized, double-blind, placebo-controlled, six-month studies of subjects with heavy menstrual bleeding associated with uterine fibroids (study 1 and study 2).[1,3] Heavy uterine bleeding was defined as at least two menstrual cycles with greater than 80 mL of menstrual blood loss (MBL). Sixty-eight percent of subjects were African American, a median age of 43 years, and reported a mean MBL of 240 mL/cycle. Subjects were randomized to elagolix-EN (study 1, n = 206; study 2, n = 189) or placebo (study 1, n = 102; study 2, n = 94). The primary endpoint was achievement of < 80 mL MBL at the final months or ≥ 50% reduction in MBL volume from baseline.

In study 1, 68.5% were responders compared to 8.7% for placebo. Responders were 76.5% and 10.5%, respectively, in study 2. Difference was observed in month 1 (mean MBL reduction vs. placebo of 120 mL), peaked by month 2, and maintained through the six-month study. Nearly 60% of subjects experienced no bleeding compared to 4% to 5% for the placebo-treated group

(mean reduction vs. placebo at six months of approximately 210 mL). Fifty percent to 62% of subjects with baseline Hgb ≤ 10.5 g/dL reported a > 2 g/dL increase compared to 21% and 16%, respectively, for placebo-treated subjects.

CLINICAL IMPLICATIONS

Uterine fibroids are a common, benign pelvic tumor in women (age 35 to 49 years) that can cause heavy menstrual bleeding, pain, bowel and bladder problems, and infertility.[2] African American women experience symptoms more often, and those symptoms often are more severe.[4,5] In addition, Hispanic women report significant symptom severity.[5] The primary treatment option is surgery (i.e., hysterectomy). Approximately 70% of women diagnosed without a hysterectomy used pharmacologic treatment.[5] Overall, relief from heavy bleeding was cited as the most important treatment goal. Currently, there are no FDA-approved non-surgical options. Based on a large administration claims database, most U.S. women took short-acting reversible contraceptive steroids as first-line treatment for heavy menstrual bleeding.[6] However, only 14% continued their initial medication, while the rest either switched from or discontinued the initial medication. Elagolix-EN is the first FDA-approved pharmacologic option that effectively reduces menstrual bleeding associated with uterine fibroid and may fill an unmet need. The cost for elagolix-EN is $907.39 for a 28-day supply. ■

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CME QUESTIONS

1. **Should angiotensin-converting enzyme inhibitors and angiotensin receptor blockers be discontinued in light of the COVID-19 pandemic?**
   a. Yes, in all patients, regardless of COVID-19 infection status.
   b. Yes, in all patients deemed to be at high risk of COVID-19 infection.
   c. Yes, in patients with COVID-19 infection.
   d. No, there are observational data that did not demonstrate harm.

2. **What was a main observation found in the study by Grein et al in the use of remdesivir for patients with severe COVID-19?**
   a. Improvement in severity of symptoms
   b. Reduction in viral load
   c. Improvement in oxygen support
   d. Improvement in shock parameters

3. **In serial studies that were conducted over four years, the reproducibility of white coat and masked uncontrolled hypertension was:**
   a. equivalent to completely uncontrolled hypertension.
   b. equivalent to completely controlled hypertension.
   c. better in men than women.
   d. poor.

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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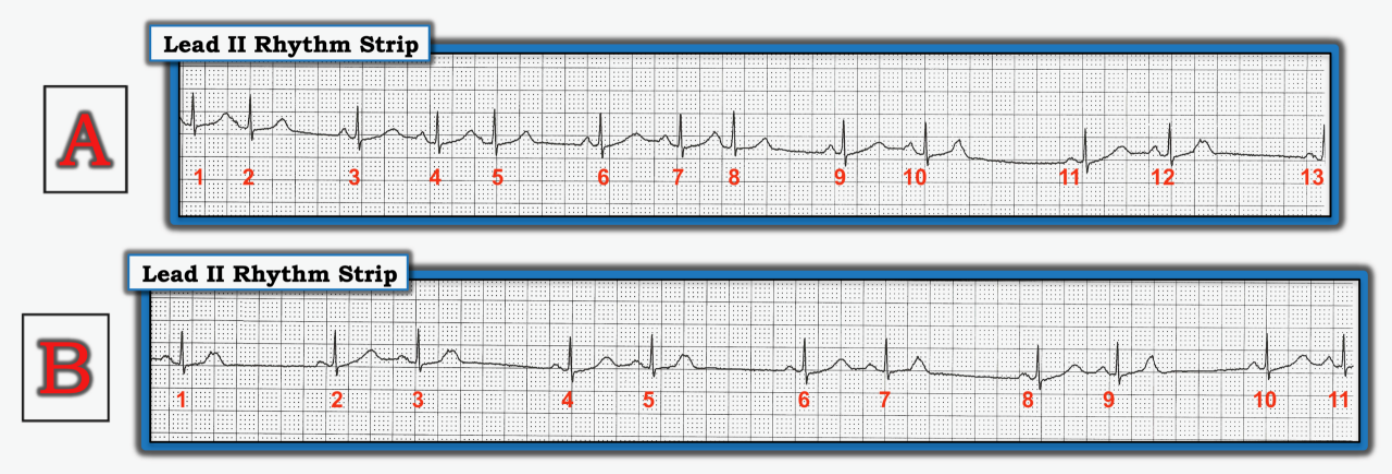
Dr. Grauer reports no financial relationships relevant to this field of study.

Group Beating from Wenckebach?

The two rhythm strips in the figure below were recorded just a few minutes apart. There is group beating. Is the rhythm the result of atrioventricular (AV) Wenckebach (second degree AV block, Mobitz Type I)?



The presence of group beating often is a tell-tale clue the rhythm in question is the result of some type of Wenckebach conduction. In both rhythm strips shown in the figure, there is group beating, either in the form of two-beat or three-beat groups. Despite this, no form of AV block is present in either tracing.

Two of the most characteristic features of AV Wenckebach are: the atrial rate is regular (or at least almost regular) and there is progressive increase in the PR interval until a beat is non-conducted, after which the cycle begins again. Neither of these characteristic findings is present in the figure.

Using calipers greatly facilitates recognition of the mechanism of the arrhythmia in the figure. It should be readily apparent that the P-P interval is the same in rhythm strip A using the P waves prior to beats 3-4, 6-7, 9-10, and 11-12. Similarly, the P-P interval is the same in rhythm strip B, if one uses the P waves prior to beats 2-3, 4-5, 6-7, 8-9, and 10-11. By setting calipers to this P-P interval distance, it should be immediately apparent that sinus P waves are missing in multiple places in these two rhythm strips.

A key to the rhythm diagnosis is to determine the appearance of a "normal" ST-T wave. To do so, look at the ST-T wave of beats 3, 6, 9, and 11 in A and beats 2, 4, 6, 8, and 10 in B. Note how smooth the ST-T is for each beat.

Is the T wave of all other beats on these two tracings deformed (usually by a notch)? The reason for this deformity is that a premature P wave (i.e., a PAC) is hiding within (and notching) the T waves of beats 1, 4, 7, 10, and 12 in A and the T waves of beats 1, 3, 5, 7, and 9 in B. The PACs that notch the T wave of beats 1, 4, and 7 in A are conducted. However, none of the other PACs are conducted, which accounts for the slight pause that follows beats 10 and 12 in A and that follows beats 1, 3, 5, 7, and 9 in B.

It turns out that after every two sinus beats, a PAC occurs. This defines the underlying rhythm as atrial trigeminy in which some PACs are conducted, and others are dropped. There is no AV block.

For more information about and further discussion on this case, please visit: https://bit.ly/37mK6ba.