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Role of Contrast Echocardiography in Screening for Pulmonary Arteriovenous Malformation in Patients With Hereditary Hemorrhagic Telangiectasia

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instances, antibiotics could be avoided. Similarly, if viruses are copathogens, then therapy could potentially mitigate the severity of illness or even prevent the development of a bacterial superinfection. However, if the viruses are simply colonizers, as suggested by the 7.1% recovery in the control population when NAAT methods were used, then it is unclear if antiviral therapy would have a benefit when these colonized patients develop CAP.

The data from the study by Lieberman and colleagues¹⁰ are provocative because they have demonstrated that when NAAT methods are used, there is a high frequency of viral detection in patients with lower respiratory tract infection. With the availability of new diagnostic tools, such as NAAT, we will now be able to ask questions about the clinical relevance and impact of respiratory viruses. We might be able to combine a positive test for a respiratory virus with the measurement of a serum biomarker, such as procalcitonin, in patients with radiographic CAP to define individuals who can be managed without antibiotics. New diagnostic tools for viral respiratory tract infections might also encourage the development of new antiviral therapies that could be effective in improving patient outcome. Thus, the currently available data have shown that viruses are commonly present in patients with CAP and that they can cause harm, yet in clinical practice we rarely try to diagnose their presence. This may change once these new diagnostic tools become more widely available, especially if they help us define an etiologic role of these pathogens and if they encourage the development of new and effective antiviral therapies.

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Role of Contrast Echocardiography in Screening for Pulmonary Arteriovenous Malformation in Patients With Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is a hereditary disease characterized by the widespread development of telangiectasias and arteriovenous malformations (AVMs). The most frequent genotypes are due to mutations in ENG (HHT1) or ACVRL1 (HHT2). AVMs are most commonly seen in the liver, lung, and brain. The incidence of pulmonary AVM (PAVM) varies widely depending on the screening technique and the underlying genotype. Because PAVMs are associated with significant morbidity if untreated and embolization therapy is highly effective, accurate diagnosis is important.^{1,2}

During the past decade, transthoracic contrast echocardiography (TTCE) with agitated saline contrast

has become the standard screening procedure for PAVM in patients with HHT¹ based on its ability to detect intrapulmonary right-to-left shunt (RLS). When injected into a peripheral vein, echocardiographic contrast appears as a white cloud of echoes against a normally black anechoic background. These microcavitations are normally filtered out by the pulmonary capillary bed, such that their immediate appearance in the left side of the heart indicates intracardiac RLS, whereas a delayed appearance indicates intrapulmonary RLS.

In this issue of *CHEST* (see page 833), van Gent and colleagues³ present a detailed analysis of TTCE and noncontrast chest CT scan in the evaluation of 252 patients who had genetic testing for suspected HHT. One hundred eighty-nine patients (74%) were genetically confirmed to have HHT. TTCE was 100% sensitive for the detection of PAVM in patients with suspected HHT. Fifty-nine percent of patients with HHT had positive TTCE, 37% had visible PAVM on chest CT scan, and 17% had PAVMs that were of a size amenable to embolization therapy. A simple quantitative grading system was highly predictive of which patients would have treatable PAVM. Also, patients with HHT1 were much more likely than patients with HHT2 to have a positive TTCE (85% vs 35%) and were also more likely to have grade 3 RLS (complete opacification of the left ventricle) on TTCE (46% vs 8%) and treatable PAVM on chest CT scan (32% vs 3%).

It is interesting that 6.7% of all patients had a patent foramen ovale (PFO) on TTCE, but none of the patients with HHT had concomitant PFO and PAVM. If one assumes that the presence of PAVM and PFO are independent events, five of their 189 patients with HHT would be expected to have both ($0.067 \times 0.37 \times 189$). This result differs significantly from their actual finding of zero ($P < .025$ by χ^2). This may simply represent sampling error but may also indicate some pathophysiologic relationship between PFO closure and PAVM development in patients with HHT.

This is a well-written article with many strengths, including a large number of patients, genetic testing in all patients, use of a quantitative grading system, and use of chest CT scan as the gold standard in 98% of patients. There are several minor limitations that are unlikely to affect the overall conclusions. Because HHT is expected to affect 50% of children, the finding that 74% of their population had HHT suggests some degree of ascertainment bias. Also, the use of a delay of more than four cycles to diagnose intrapulmonary RLS may have underestimated the true incidence of PAVM, since other studies have confirmed PAVM in patients with a delay of two to three cycles.^{4,5}

Based on this and other recent studies, how should we screen for PAVM? It is almost universally agreed

that TTCE should be the initial screening test in patients with suspected HHT.¹ Although sensitivity was only 92% to 94% in older studies,^{6,7} these studies were retrospective or did not use a uniform gold standard. Combining all three reported prospective series gives a sensitivity of 98.6% (137/139).^{3,6,8} TTCE has been variably defined as positive for intrapulmonary RLS based on a delay of more than three,⁶ four,⁷ and more than four³ cardiac cycles before contrast appears in the left ventricle after its appearance in the right heart. Barzilai and colleagues⁵ found that patients with PAVM had a mean RLS delay of 2.7 cardiac cycles with a range of 1.4 to four cycles, whereas 10 patients with atrial septal defect showed RLS within 1 s (about 1.5-2 cardiac cycles). Zukotynski and colleagues⁴ found a mean delay of six cardiac cycles with a range of three to 10 for those who had PAVM. I recommend using a delay of three cardiac cycles as the low threshold for intrapulmonary RLS and two cycles as the upper threshold for intracardiac RLS. Two to three cycles should probably be considered indeterminate.

Should we grade the severity of intrapulmonary RLS, how should we grade it, and what should we do with a grade 1 RLS? I prefer the quantitative systems described by Gazzaniga et al⁸ and van Gent et al,³ which use < 20 and < 30 bubbles, respectively, as the upper limit for a grade 1 RLS. Both quantitative systems have a negative predictive value of 100% for the presence of treatable PAVM and good interobserver agreement.^{3,8} Several authors have pondered whether we should defer chest CT scan in patients with grade 1 RLS unless their grade increases but ultimately concluded that they did not have enough data to recommend a change.^{3,4} However, Gazzaniga and colleagues⁸ seemed to favor a change based on their additional data. If one combines the data from the three studies that graded TTCE and used CT scan as a gold standard, there are a total of 144 patients with confirmed or suspected HHT who had a grade 1 RLS by TTCE.^{3,4,8} Ten patients (6.9%) had PAVM on CT, whereas none had treatable PAVM. When no events are observed in a trial, the "rule of three" states that "we can be 95% confident that the chance of this event is at most three in n."⁹ Therefore, the upper limit of finding treatable PAVM with a grade 1 study would be 2.1% (3/144),^{3,4,8} which is identical to the upper limit of finding a treatable PAVM if the TTCE is completely negative (3/148).^{3,8} Since we are already comfortable deferring chest CT scan when TTCE is negative,⁴ the above figures tell us that we should be no less comfortable deferring it with a grade 1 RLS.

Besides the cost of chest CT scan, there is a risk of radiation-induced cancer. A recent article quantified the effective dose of radiation delivered during various CT scan procedures and used data from the

Biologic Effects of Ionizing Radiation report to determine the lifetime attributable risk of cancer.¹⁰ Risks were greatest for women and younger patients. I was stunned to read that one out of every 330 20-year-old women who had a chest CT scan to rule out pulmonary embolism is projected to die of radiation-induced cancer, although the risk could be as high as one out of 90 with a poorly designed imaging protocol.¹⁰ If we were to defer chest CT scanning in all patients with negative TTCE or a grade 1 RLS, chest CT scan could be avoided in 303 out of 442 (69%) patients in the studies by Gazzaniga et al⁸ and van Gent et al.³ This would represent a tremendous cost savings and approximately one less death from cancer. At a minimum, we should weigh the pros and cons of deferring chest CT scan in each such patient by considering factors such as age, sex, number of bubbles seen, family history of cancer, and patient preference. If we proceed with CT scan, we should use a protocol that minimizes radiation exposure while finding all treatable PAVM.

Finally, this study found that 6% of patients without HHT had positive TTCE.³ The international guidelines for diagnosis of HHT¹¹ list PAVM as a diagnostic criterion, but do not specify what “counts” as a PAVM. According to the current study, a positive TTCE had a positive predictive value of 97% (112/116) for the correct diagnosis of HHT, whereas a grade 1 RLS had a positive predictive value of only 91% (32/35).³ Although I believe that the data support a grade 2 or 3 RLS standing on its own as a criterion for the diagnosis of HHT, the diagnostic significance of a grade 1 RLS in the absence of a positive chest CT scan is less certain.

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Percutaneous Coronary Intervention in Anticoagulated Patients and Balancing the Risk of Stroke and Bleeding

To Interrupt or Not To Interrupt?

Coronary artery disease coexists in 20% to 30% of patients with atrial fibrillation (AF),¹ and some will inevitably require coronary angiography and percutaneous coronary intervention (PCI). Performing PCI in this cohort of patients is often challenging because many are taking oral anticoagulation for thromboprophylaxis, usually in the form of warfarin. Two important issues must be considered: first, whether to interrupt or continue anticoagulation during the periprocedural period; second, the choice of long-term antithrombotic therapy to follow PCI.

The first of these questions is addressed in this issue of *CHEST* (see page 840), as Jamula et al² present a meticulously performed systematic review and metaanalysis of the safety of uninterrupted anticoagulation in patients requiring elective coronary angiography and PCI. This is important because stopping anticoagulation exposes patients to the risks of thromboembolism, and reinitiation may cause a prothrombotic state due to protein C and S suppression.³

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