## expert roundtable »

# The Role of Cardiopulmonary Exercise Testing (CPX) in Research of Chronic Heart Failure and in Treatment Decisions

Moderated by **William Kraus, MD**[1]
Discussants: **David Whellan, MD**[2] and **Jonathan Myers, PhD**[3]

*The following Expert Roundtable Discussion was held on October 22, 2010. Dr. William Kraus from the Duke University Medical Center moderated the topic "The Role of Cardiopulmonary Exercise Testing (CPX) in Research of Chronic Heart Failure and in Treatment Decisions," with Drs. David Whellan from the Jefferson Coordinating Center for Clinical Research, and Jonathan Myers from the Palo Alto VA Hospital.*

The discussion focused primarily on: (1) standards of care for heart failure patients, including surgery, mechanical support and prescriptions, (2) the use of VO2 as a parameter of measurement, (3) expert use of and training for the testing systems and variability of results, (4) creation of a testing facility and the American Heart Association Scientific Statement "A Clinicians' Guide to CPX Testing", (5) detecting primary cause of cardiomyopathy, (6) the complementary use of pulmonary function testing, (7) examination of the CPX test results and its various parameters, (8) the role of CPX testing in clinical trials. (*Med Roundtable Cardiovasc Ed.* 2010;1(4):243–249) 

**TRIALS DISCUSSED:**
HF-ACTION

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**DR. KRAUS:** I'm Bill Kraus from the Duke University Medical Center, the Medical Director of Cardiac Rehabilitation and in charge of a laboratory for cardiopulmonary exercise testing, such as we did for the recently completed Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) Study. We're here to discuss the role of cardiopulmonary exercise testing, which we will be referring to as CPX testing, in both cardiovascular care for individuals with heart failure, as well as in clinical trials that test both interventions and medical devices for the treatment of heart failure. I have with me today Dr. Dave Whellan, who is Associate Professor of Medicine at Jefferson Medical College and the Director of the Jefferson Coordinating Center for Clinical Research and also the co-principal investigator of the HF-ACTION study, and Dr. Jon Myers at the VA Palo Alto Health Care System in Palo Alto a Clinical Professor at Stanford University who also directs the exercise research laboratory at the VA Hospital in Palo Alto.

As we all know, CPX testing has been used for a number of years to define clinical characteristics for certain procedural interventions for individuals with heart failure and to assess clinical status. It has also been used as a benchmark for physiologic outcomes or intermediary outcomes in clinical trials particularly with device therapy. Whether CPX testing is necessary and what additive value it provides in these settings has become somewhat controversial in the last several years. I thought a discussion of these issues may be of interest.

I'll start with you, Dave. What do you believe are the standards of care for heart failure patients for which this type of testing is desired or required?

**DR. WHELLAN:** I think what's important to understand is that CPX testing has been a major component of research with heart failure patients and has migrated into the clinical care of heart failure patients. For those who aren't familiar or who don't perform CPX testing, I think there's always a question about its utilization; is it necessary or useful?

One thing I'd like to address early on is that this is a safe procedure. The information coming out of the HF-ACTION study, where we had more than 2,000 subjects performing over

| Definition of Terms | |
|---|---|
| Peak $VO_2$ | Minute volume of $O_2$ utilization; relative peak $VO_2$ is expressed in units of mL/kg/min. |
| $VE/VCO_2$ slope | The slope of the linear relation between minute ventilation (VE) and $CO_2$ production; and indicator of ventilatory efficiency. |
| End-tidal $CO_2$ pressure | The partial pressure of carbon dioxide output at the end of an exhalation. |
| MVV | Maximal voluntary ventilation. The upper limit of the body's ability to inhale and exhale air, expressed as liters/minute. |
| FEV1 (Forced Expiratory Ventilation, 1 second) | The forced amount of exhaled air in the first second after deep inhalation. |
| FVC (Forced Vital Capacity) | The maximal amount of air that can be exhaled after deep inhalation and maximal exhalation. |
| RER (Respiratory Exchange Ratio) | The ratio of carbon dioxide production to oxygen uptake during exercise. |
| $O_2$ pulse | $VO_2$/Heart Rate; represents an estimate of the cardiac output at any given stage during a progressive exercise test. |
| Dyspnea Index | VEmax/MVV; an indicator of ventilatory reserve. |

6,500 CPX tests was that there was a very low adverse events rate. HF-ACTION was a randomized controlled clinical trial designed to investigate the effectiveness of exercise training in in 2,331 individuals with Class II-IV heart failure. There were no deaths that were related to the testing. The rate of non-fatal cardiovascular events was 0.5 per 1,000 tests. I think it's important for people to understand the test that we're talking about, putting a patient with cardiomyopathy on a treadmill, and measuring their pulmonary function at the same time, is a safe test.

We utilize CPX testing in clinical practice—I'm going to move away from the research for a moment— as a tool to better understand the physiology and prognosis of the patient. I've used it in quite a few of my patient populations to better define disease severity and to understand drivers of symptoms. As clinicians know, it can be difficult interpreting a patient's symptoms, and when trying to understand how much of this is the pathophysiology of the heart, CPX testing can be extremely useful.

CPX testing yields data that are not just related to heart function but also to other physiologic abnormalities that can occur in these patients. This type of testing can link the symptoms to the disease severity and address some of the issues that we're always struggling with in the clinic, such as whether or not a patient needs more intensive treatment or to be on disability.

With respect to prognosis, we use CPX testing to evaluate patients for consideration of cardiac transplantion or mechanical circulatory support. Certain interventions are indicated for those patients whose test results are below certain cut points. It used to be peak $VO_2$s of 14 mL/kg/min. We've moved these cutoffs a bit lower through the use of beta blockers. When patients get into that low range, one needs to begin thinking more seriously about the option of transplantation or mechanical support, because their prognosis without those interventions is quite dismal.

We've used CPX testing when thinking about exercise prescriptions. It was used in the HF-ACTION study to screen subjects prior to initiating an exercise regimen. When patients were on the treadmill, we examined ischemia burden, arrhythmias, and we used the findings to make the prescription for the exercise intervention. I think it's got great potential, particularly when trying to understand patient physiology and, as we'll talk in a little bit, in terms of managing the patient clinically.

**DR. KRAUS:** There has been a lot of emphasis on the peak oxygen consumption or peak $VO_2$ as a parameter of measurement with CPX testing. Jon, aren't there other parameters derived from the study that can be clinically useful as well as for research?

**DR. MYERS:** Yes. I think there have been a considerable number of studies, in the last decade in particular, regarding some of these other measurements, particularly ventilatory inefficiency that have been shown to be, in most of these studies, better markers of risk than peak $VO_2$. This is somewhat controversial, but we've actually gone to using combinations of peak $VO_2$ along with other markers of ventilatory inefficiency in our work. In particular, the $VE/VCO_2$ slope has been the most commonly used among others. From our data and from other studies that have looked at this and done follow up studies, you derive a more accurate estimate of risk by using a combination of CPX variables.

**DR. KRAUS:** How hard are these other variables to measure? Do you have to have a trained laboratory technician to do that? How much confidence can you give in the parameters one obtains from routine CPX testing?

**DR. MYERS:** The main variables, such as the $VE/VCO_2$ slope, which is the most commonly used marker of ventilatory inefficiency, are automatically provided by most systems. It's really easy to measure. If the system doesn't provide it automatically, it's easy enough to put two columns of data into a spreadsheet and calculate it.

There are other parameters, such as the lowest $VE/VCO_2$ ratio or end-tidal $CO_2$ pressure at rest and during

exercise. The oxygen uptake efficiency slope is another one that takes a little bit more effort and time to calculate. Another marker of ventilator inefficiency is oscillatory breathing, though this is a little more complex and most clinicians won't take the time to measure it. We have encouraged the manufacturers of the metabolic systems to include these other measurements in their systems to make it easy for the clinician or the technician to apply.

**DR. WHELLAN:** Bill, I want to respond to part of your question, with respect to required expertise and understanding of the systems. I do think there is value in having expert groups like your core lab and Jon's group, people who are familiar with these systems and the testing procedures, provide CPX testing. There is a certain amount of quality control that's needed for maintaining the systems, for evaluating the test results and providing feedback to clinicians in terms of how to interpret the results. We saw that in the HF-ACTION study when we had a number of centers participating in the study. Your group examined each center's testing and provided feedback on the quality of the studies. There were variations across sites in quality and there was a learning curve in performing tests during the trial.

**DR. KRAUS:** You're talking about variation across sites in their ability to obtain the data and interpret the results.

**DR. WHELLAN:** Right, and I think this translates into clinical practice. I would caution a clinician without the training and understanding of the testing systems to go out and set up a CPX lab. I think there is an expertise that's necessary for testing and interpretation, and that a clinician may be better served by referring patients for CPX testing and interpretation.

**DR. MYERS:** Dave, I would like to add to that. I think that's one of the things that has hindered the application of CPX in the clinical trials, especially for multi-center clinical trials. The HF-ACTION trial experienced this, I know, so you and Bill as much as anyone know some of the pitfalls of trying to apply the CPX test in a multi-center trial. We've been the CPX core laboratory for much smaller trials that were using peak $VO_2$ as an outcome measure. There are significant problems with just the required technical training for the metabolic measurements and interpretation in using CPX testing.

**DR. KRAUS:** Before we get back to more details about the clinical and research applications, can I ask you, Jon, to talk a little bit more or expand a little bit more about what kinds of training is required to actually run these laboratories? Are there professional standards for this kind of activity?

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>
> *~ David Whellan, MD*

**DR. MYERS:** There are professional standards; the American College of Sports Medicine, for example, has certification programs for exercise physiologists for testing. The issue is, quite often, that a nurse or even a technician is in the lab and the principal investigator in a multi-center trial is usually pretty physically remote from the exercise lab and the ongoing testing, so that PI oversight is generally not hands-on. I imagine that's been the experience you two have had as well.

One thing that I think has been helpful is that the American Heart Association has produced scientific statements on exercise testing and CPX testing, in particular. There exist exercise testing guidelines, which we require all of our cardiology fellows to read, although I think academic programs don't often do that. I think that that's very important for application of the exercise test in general, but in addition there exists the AHA statement on functional capacity that was published in its revised form in 2007. Another valuable AHA scientific statement entitled "Recommendations for Clinical Exercise Laboratories" involves how to appropriately set up and run an exercise testing laboratory.

This year, the AHA published "A Clinicians Guide to CPX Testing." It contains very basic information about how to run and get a valid exercise test and includes the details that the clinician or the technician needs to know before they do a cardiopulmonary exercise test. As doing CPX testing does require some expertise and may not be practical in many physicians' practices, I think it is important that labs participating in a clinical trial have significant experience with CPX testing. I believe that understanding the guidelines and having some experience goes a long way.

**DR. KRAUS:** Jon, just to follow up on that: If you were to set up a CPX laboratory not for a clinical trial, but for clinical care, to what kinds of considerations would you pay a lot of attention? Where could one get help or advice? For example, what kind of metabolic cart to buy? What manufacturer, for example, or cart upkeep, or calibrations and that type of thing? How does one proceed through those considerations?

**DR. MYERS:** First of all, I would recommend that one read the AHA Scientific Statement for clinical exercise laboratories. It's a really nice document because it starts with the lab environment, the equipment, and the technical expertise required. It goes over

calibration of the system, and the applications of the CPX unit.

Then, if one is going to do CPX testing, then I'd recommend that they read the "Clinicians' Guide to Cardiopulmonary Exercise Testing in Adults," which the AHA published this year. There are other statements, as well, from the American Thoracic Society, and the American College of Sports Medicine. There's a European working group on rehabilitation and exercise physiology that has done a great job putting several related documents together about CPX testing. As a start, I'd recommend that someone read these.

As far as a metabolic cart, it feels like I'm asked that question constantly. "What is the best cart? What should I use?" Before they are allowed to be purchased by hospitals, all of these carts undergo approval by the FDA. They all have calibration routines that ascertain that the information obtained is pretty reliable.

Due to the competition between the manufacturers of metabolic testing systems, they all do a good job in providing good information. However, the user needs to know and be able to recognize when that information may not be quite right and know what to do when it isn't. When to start a test over, when to discard a test, things like that are always important considerations when one is doing a CPX test.

**DR. KRAUS:** Of course; the oversight functions are provided by a core lab in a clinical trial, for example. Isn't that right?

**DR. MYERS:** Yes, exactly. I think that's the purpose of a core lab. As you know, it provides a blinded objective view of the information and interpretation of the information. Plus, they have the experience and expertise to provide appropriate oversight and ensure uniformity of the reported results and to identify problems that might not be identified by a single site in isolation. I think that's very useful for multi-center clinical trials.

**DR. KRAUS:** Getting back to something that you brought up, Dave, which is understanding the physiology and the clinical status of patients with cardiomyopathy. Doesn't it sometimes arise where one is concerned about whether the primary cause or dyspnea on exertion is pulmonary versus cardiac in origin? How might a CPX test help in that situation?

**DR. WHELLAN:** Generally the heart failure patient population has multiple comorbidities including COPD and peripheral vascular disease. The CPX test can actually help in terms of looking at patients' cardiac limitations relative to these comorbidities. Parameters of importance are how long patients were able to exercise on the test, and how hard patients were able to push themselves relative to the CPX test parameters. The test is used to see how much of their limitation is due to the ability to move blood and oxygen through the body and extract that oxygen, implying a cardiac limitation, compared to a problem where the patient is limited primarily by pulmonary, vascular or general deconditioning. For instance, one can assess the dypnea index for an indication of pulmonary limitation and $O_2$ pulse as an indicator of cardiac limitations.

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>
> *~ Jonathan Myers, MD*

It's a nice way of teasing out the relative importance of comorbidities in terms of functional capacity. A lot of times we blame everything on cardiomyopathy, when in fact these patients might be limited in functional capacity for other reasons, and the CPX test can help sort that out. That plays a very important role, obviously, in considering a patient for cardiac transplantation, where the care provider has to consider the impact of numerous procedures, risky surgery, and a lot of resources directed at treatment of the cardiomyopathy. At the end of the day, the patient may not feel better and have no significant improvement in their quality of life if the comorbidities, which are not addressed by the intervention, are identified as major contributors to symptoms and are not taken into account. One might be sorely disappointed by lack of benefit in a successful surgery because it has not addressed a major issue of functional limitation due to comorbidites.

**DR. KRAUS:** Yes, that's interesting. Jon, any further comment on that? Also, for a clinical test, do you routinely do pulmonary function testing before the CPX test?

**DR. MYERS:** We do, and I think that is valuable, not only because it's easy to do, but because it provides valuable clinical information. In a routine clinical CPX test in a cardiology department, it just takes a couple of minutes. One can do three trials to obtain the MVV, FEV1 and FVC. If one observes or suspects a more serious pulmonary problem as a consequence, one can send the patient to a pulmonary specialist for further evaluation. At a minimum, it provides an assessment at baseline of whether a patient may primarily be limited by pulmonary disease. It also allows one to measure what's called the breathing reserve during exercise, which is a valuable marker of whether a patient is limited primarily by cardiovascular disease or pulmonary disease. So, one needs to have the resting MVV and FEV1 to make that determination.

I would add to that, Bill, as well. I view and try to teach that in interpreting a clinical CPX test, one should

look at the entire test as a whole. There's a tendency to examine and focus on only one's favorite variable, whether that's $VO_{2\ max}$ or one of the newer ventilatory inefficiency markers. The pulmonologist, for example, the person who focuses on the CPX, tends to ignore the electrocardiogram. The cardiologist tends to ignore the CPX part of the test due to undue focus on the ST segment responses. I believe that we need to focus on the entire test, and in that sense, the CPX provides a valuable and broad range of clinically useful information.

There's an enormous amount of diagnostic and prognostic information available for the clinician even before the exercise portion of the test starts. Some of the metabolic cart manufacturers have done a nice job including overall risk estimates, including pretest risk estimates as part of the pretesting assessment, using known clinical variables or demographic characteristics. Then, once the test is completed the exercise testing information provides post-test diagnosis and estimates of prognosis.

**DR. KRAUS:** Let's talk about that issue for a few minutes. Jon, you alluded to the maximal ventilatory volume on a baseline pulmonary function test. If a person gets to the maximal part of their test and is at maximum ventilatory volume, then that implies that there's sort of a pulmonary limitation to peak exercise, doesn't it?

**DR. MYERS:** Correct. We do that, Bill, simply taking the maximal voluntary ventilation at rest, which we usually estimate from the FEV1 at rest. You take the FEV1 times 35 or 40 to estimate the MVV. There's some controversy about whether one can estimate or needs to measure the MVV. In general, one can take the FEV1 times 40 and that provides an estimate of the maximal voluntary ventilation. Then one divides the maximal exercise ventilation at peak exercise by the MVV and that provides the "breathing reserve" or what's been also called the dyspnea index. Most people have a 30–40% breathing reserve at peak exercise. When someone exhausts that reserve or that they reach 90% or 100% of their MVV at rest when they're at peak exercise, then we consider that there is a significant pulmonary limitation to functional capacity. Thus, the breathing reserve, or dyspnea index, is one additional measurement that can help in evaluating the patient.

**DR. KRAUS:** Likewise, I believe that there's a parameter called the $O_2$ pulse, which is the $VO_2$ divided by the heart rate at any given time point. If the $O_2$ pulse also is limitated at peak exercise, then that implies more of a cardiac abnormality underlying peak exercise performance, is that not right?

> ***"That makes CPX testing a very efficient test to tell a lot of things about the patient…"***
>
> *~ William Kraus, MD*

**DR. MYERS:** That's correct. That's something that Dr. Karl Wasserman at UCLA has been pushing for a long time. We graph the $O_2$ pulse during exercise testing. There are some recent studies documenting that a plateau in the $O_2$ pulse response to progressive exercise is a good marker of the presence of coronary artery disease and ischemia as a limiting factor to maximal performance.

**DR. KRAUS:** That makes CPX testing an efficient test to tell a lot of things about the patient, doesn't it?

**DR. MYERS:** Exactly. There are a number of relatively simple results from the test that are very informative to the clinician. Again, the metabolic cart manufacturers have done a really good job, for the most part, of presenting this information in their clinical reports.

**DR. KRAUS:** Sometimes one has trouble on a regular graded ECG exercise test without gas exchange data in being able to determine whether or not the patient was trying hard enough or got to maximal exercise because there's such a wide variation in the peak heart rate response among individuals. Is there an objective parameter from the CPX test that we can use to determine whether it was actually a maximal test?

**DR. MYERS:** Yes. The classic one is the $VO_2$ plateau concept dating back to the 1950s; in fact, there's a 1955 article from Henry Taylor that has received an enormous amount of attention and longevity for this plateau concept. People still use that, but I think it's faded out of major practice, and for good reason. The guidelines about which we first spoke have discussed this: Most patients with heart failure, as you know, don't exhibit that $VO_2$ plateau, at least as it was originally defined or people have come to define it over the years. So, one should use other parameters to determine whether the test was a maximal effort.

I like to use a combination of parameters. The respiratory exchange ratio, or RER, is one. When the RER is more than 1.10, it provides a good indication that the patient provided a good effort. We regularly combine that with the Borg Scale rating of perceived exertion, to make sure that the patient perceived that they provided an adequate effort. Then, one can use observations of the patient during the test: whether they appeared to be sustaining a maximal effort, whether walking efficiency had begun to deteriorate and other observed parameters. Those are the three parameters that we use to determine maximal effort. Peak heart rate also can be useful, but might be misleading as well, as we discussed, because of the wide standard deviation in

the age-predicted maximal heart rate equations across populations. Then, of course, many of the coronary and heart failure patients whom we test are often on beta blockers and this affects the maximal heart rate response to progressive exercise testing. So, one has to be careful about using the maximal heart rate response to exercise testing as a reliable parameter of peak effort in clinical cardiology populations. Using a combination of parameters, one can get a pretty good sense of when the patient has given a maximal effort.

**DR. KRAUS:** It sounds like with a good lab and a little bit of training and education, one can obtain a lot more information from CPX testing than we might have at first thought when focusing only on the peak $VO_2$ and that this additional information can actually can help with management of patients. Do both of you agree on that?

**DR. WHELLAN:** Absolutely.

**DR. MYERS:** Yes, I agree. I think we need to push the concept of using all of the available information obtained during a progressive exercise CPX test: The rest, exercise, and post-exercise information are all important. For example, there is heart rate recovery. Some have been advocates of $VO_2$ measurements in recovery and the ST segment response in recovery is also important for diagnosis and prognosis. Many people ignore or miss those parameters, simply because once the exercise part of the test is over they take the electrodes off and ignore the additional information. But using all the test information together can really enhance the test performance.

**DR. KRAUS:** Now, I'm going to direct a question to both of you regarding the role of CPX testing in clinical trials. Specifically, I'd like to have some comments about device approval by the FDA because, as we all know, it is used as a surrogate outcome for improvement in functional capacity in a number of device trials as well as clinical intervention or pharmaceutical trials. There's been controversy about whether the expense of the test is appropriate or needed and whether or not one can do a simple test like a six minute walk as a substitute.

Let's talk a little bit about the different kind of information that's gained from the two and whether or not we think CPX testing should be an important part of all trials of clinical heart failure. First, Dave, I'll turn to you.

**DR. WHELLAN:** I think the issue of the six minute walk versus the CPX study is an important one. The selection of one test compared to the other can be determined by trial mechanics and the ease of doing one versus the other and the issues of quality that we've talked about. However, I think it's important to emphasize that they're really measuring two different characteristics of the patient. The six minute walk is a measurement of low-level functional capacity and submaximal endurance, whereas the CPX test is one of maximal exercise capacity. Now, for some heart failure patients, the six minute walk can be a measurement of maximal exertion. However, typically, it's really directed at something different from the CPX, which is measuring a maximal performance. The two tests do correlate. However, I think people look at that correlation and jump to a conclusion that one can be substituted for the other. I really don't think that's the case.

In terms of the importance of the CPX test as a surrogate outcome measure, I think it's very easy to point to some examples where peak $VO_2$ has improved with an intervention in early studies, but that there has been a disassociation with the clinical outcomes when those therapies have been evaluated in larger studies. I would point particularly to clinical trials of inotropes in heart failure, as an example. But, in device studies, peak $VO_2$ has been very consistent as a surrogate marker and has translated into clinical benefit when studied in larger trials. So, there is a risk that peak $VO_2$ may not be a perfect surrogate outcome measure for important clinical hard outcomes in heart failure studies. However, the reality is that doing large clinical trials, even in the heart failure population, requires a very large amount of resources and time and is not going to be sustainable. We're likely to be moving into an environment where studies that use markers like peak $VO_2$ get the initial approval for the intervention of device. As we are seeing now, phase four clinical registries, patient registries, would be used to evaluate safety.

**DR. KRAUS:** Jon, did you want to add anything to that?

**DR. MYERS:** Just a quick comment: I think the use of peak $VO_2$ that directly measures someone's oxygen uptake has been shown repeatedly over several decades of studies to be more accurate and reproducible than measuring someone's treadmill time on a graded exercise test with only ECG monitoring. Treadmill time can be a very misleading measurement, as we know. Many patients get on the treadmill and with repeat testing just walk longer due to accommodation to the environment of the test. That is less likely to occur when one can objectively measure the patient's physiologic response directly using gas exchange.

There's no really accurate surrogate for functional capacity other than peak $VO_2$. As a clinical endpoint, CPX testing is the gold standard for cardiopulmonary function. The correlation with peak $VO_2$ and six minute walk performance is anywhere between 0.4 and 0.8, and typically in the range of 0.5 to 0.7. You can see there's some limitation to substituting one for the other.

There are other surrogates, such as functional questionnaires, that don't necessarily relate that well to someone's performance on the treadmill. I

think that's really one of the main values of directly measuring $VO_2$. It's an accurate measure of the cardiopulmonary response. Plus, there is the wealth of information that can only come directly from the gas exchange response to the exercise test.

**DR. KRAUS:** One last question on this topic; the role of CPX testing in trials and device approvals. There's some concern among some investigators that the one limitation of the CPX test is that one can't always get individuals to a peak exercise capacity as measured by these objective measures. Is there a submaximal measure that one can get from a CPX test that might be similarly indicative of functional capacity that would not require a maximal test?

**DR. MYERS:** Yes, one of the benefits of some of the markers of ventilatory inefficiency, such as the $VE/VCO_2$ slope, is that it doesn't require a maximal effort to be of value. One doesn't have to get into the discussion that we have heard, with questions like: "Was this a true maximal effort? Let's go over the five different criteria," to determine whether this was a true peak $VO_2$. With the $VE/VCO_2$ slope and most of the other markers of ventilatory inefficiency, one doesn't need a maximal test. It's another reason to advocate the use of those markers in addition to peak $VO_2$ in a clinical trial.

**DR. KRAUS:** That's very insightful. Thank you, Jon and Dave. I believe that we've covered the landscape here: how to do a CPX test, what are good markers, the role of CPX in clinical care, how CPX testing can give us other information on the clinical status of our patients and prognosis, as well as the role of CPX testing in clinical trials. Thank you both.

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