Pulmonary Embolism Response Teams:
A New Paradigm in Pulmonary Embolism Management

Todd Wood, M.D., R.P.V.I.
Interventional Cardiology & Vascular Medicine
The Heart Group of Lancaster General Health

INTRODUCTION

Pulmonary embolism (PE) remains a commonly under-diagnosed and lethal entity. Of the more than 600,000 cases of PE per year in the U.S., it is estimated that the diagnosis is missed in up to 70% of cases, with a mortality in these patients that approaches 30%.

PE causes or is implicated in 15% of all hospital deaths. One 25 year study in the U.S. reported an annual incidence of PE related deaths of 69/100,000, or a total of approximately 200,000 deaths annually.[1,2] The incidence of death due to PE is thus higher than the combined total of HIV, motor vehicle accidents, and breast cancer.

The spectrum of PE has historically been simply divided into massive PE or non-massive PE, a dichotomy reflected in the degree of aggressiveness of therapy: systemic fibrinolytic therapy vs. systemic anticoagulation.

This dichotomization represented an over-simplification of the range of PE's clinical presentations and its associated clinical implications, and there is now increasing awareness of the category of sub-massive PE and its associated clinical markers, imaging findings, and biomarkers. This understanding, coupled with an expanding range of FDA approved therapies, has made this entity a newly intense focus for clinicians, while calling into question the prevailing and overly simplified dogma: 'unstable equals lyse and stable equals anticoagulate.' In response, Lancaster General Hospital, among a consortium of similarly minded institutions, has implemented a multi-disciplinary Pulmonary Embolism Response Team (PERT) to make rapid clinical assessments and to consistently bring to bear the full range of therapeutic options for suspected or confirmed massive and sub-massive PE's.

THE SPECTRUM OF PULMONARY EMBOLISM

The delineation of massive PE is a relatively straightforward process, with the hallmark being hemodynamic compromise defined as a sustained systolic blood pressure <90mm Hg for 15 minutes or more. Though this dramatic entity is notable for carrying a 58% mortality at three months, it represents less than 5% of the cases of PE.[3] The balance of the PE spectrum comprises 95% of cases from minor through sub-massive pulmonary embolism that have been frequently blended together in clinical practice because there was a lack of meaningfully different therapeutic approaches. But the arrival of varied therapies has again put the focus on identifying individuals at higher risk of in-hospital and 30 day mortality, as well as long term morbidity.

Of the bulk of PE cases judged non-massive by clinical criteria, 55% are deemed minor and carry a good prognosis with very low mortality, while 40% are in the gray middle ground of sub-massive PE that carries a mortality of approximately 21% at 3 months.[3] Given this high percentage of cases that still has significant mortality, sub-massive PE represents a clear area to focus on improving delineation of clinical categories and delivering more aggressive therapy when it is safe and effective to do so.

DEFINING SUB-MASSIVE PULMONARY EMBOLISM FOR PROGNOSTIC PURPOSES

Since sub-massive PE lacks the bellwether of hemodynamic instability, the focus of assessment is detection of sub-clinical cardio-pulmonary compromise. Early evidence of impending hemodynamic collapse is largely indicated by signs of a struggling right ventricle (RV), as suggested clinically by findings that include RV strain by electrocardiogram, elevated cardiac biomarkers such as troponin, acute elevation in pulmonary pressures, and RV dysfunction.

PREDICTING MORTALITY

An elevated troponin accompanying PE has been associated with an odds ratio of 4.97 for death or complications.[4] RV dysfunction in particular has been increasingly identified as a means of predicting mortality; if RV hypokinesis is present on a baseline

echocardiogram, the relative risk of mortality at three months increases by 40% (from 15% to 21%).[3]

A metric that is quickly becoming the most useful is the right ventricular to left ventricular (LV) internal diameter during diastole (RV:LV ratio). In one study, when the RV:LV ratio was < 0.9 the in-hospital morality during the index hospitalization was 1.9%; if the ratio was ≥ 0.9 the mortality was 6.6%.[5] The findings were observed to persist at three months follow up with further stratification still possible using the initial RV:LV ratio. One study showed a three month mortality of 0% with an RV:LV <1.0; 8% with an RV:LV of ≥1.0 but <1.5; and 17% with RV:LV ≥1.5.[6] Another predictor of long term survival was the resolution of right ventricular dysfunction at discharge. Unresolved dysfunction was associated with a mortality of 10.2% at 4 years, but resolution equated with a 2.3% mortality.[7]

Beyond the individual predictive capacity of these metrics, there is evidence that if there is more than one marker of RV impairment there is a higher risk. In comparison with PE patients who had normal RV and troponin, one study showed a hazard ratio for death or clinical deterioration of 7.9 for either a positive troponin or RV dysfunction alone, versus 14.2 when both abnormalities were present together.[8]

PREDICTIVE CAPACITY BEYOND MORTALITY

The predictive capacity of RV dysfunction seems applicable not only to mortality, but also to associated morbidity such as chronic thrombo-embolic pulmonary hypertension (CTEPH). RV dysfunction in the setting of PE has been associated with a 44% incidence of pulmonary hypertension at one year of follow-up, which is triple that of PE patients without RV dysfunction.[9] Importantly, the aggressive treatment of PE seemed to lower this incidence of pulmonary hypertension. One study demonstrated a post therapy reduction in pulmonary artery pressures and pulmonary vascular resistance with fibrinolytics but not with anticoagulation alone. These patients were followed a mean of 7.4 years, with the fibrinolytic group demonstrating no exercise-induced changes in pulmonary pressures/resistance, while the anticoagulation group did have elevations with exercise.[10]

LIMITATIONS OF STANDARD THERAPY

Historically, the benefit of fibrinolytic therapy has been counterbalanced by the incidence of bleeding events. Intracranial hemorrhage, the most feared complication, has been observed in 3% of patients in the ICOPER trial and 2% in the more recent PEITHO trial.[3,11] Efforts to improve the risk/benefit ratio have focused on delivering lower doses of fibrinolytic drugs over longer periods of time. Efforts to deliver a continuous infusion of a fibrinolytic agent through a catheter with multiple side holes placed directly in the clot did show modest improvements in complication rates, but bleeding remained a frequent enough phenomenon to limit the wholesale acceptance of this approach.

NOVEL THERAPIES

More recently, newer technologies have demonstrated much improved safety profiles earning them FDA approval for use in pulmonary embolism and have re-invigorated the discussion about maximizing therapy in the most at-risk patients.

A. EKOS—ULTRASOUND ASSISTED FIBRINOLYSIS

The EKOS catheter (Ekos Corp; Boswell, WA) is also a multi-side hole catheter for delivering directed fibrinolysis, but with the addition of a core ultrasound wire that emits ultrasound energy at each of the drug infusion points. This energy adds the effects of direct fibrin unwinding without fragmentation, as well as a phenomenon known as acoustic streaming that enhances drug delivery and penetration. The net effect is that more drug is delivered directly into the clot burden, which allows for lower drug delivery doses. The catheter can be used effectively at half the infusion rates and duration of traditional approaches. Infusion rates of tissue plasminogen activator (tPA) of 0.5-2mg/hr are typical for this device and total doses in the trial to date have usually been 24mg over 12-24 hours.

Several small studies that used this approach demonstrated significant clinical efficacy with satisfactory safety, which prompted the more robust and recently published SEATTLE II study in which 150 patients with massive and sub-massive PE underwent intervention with the EKOS catheter. The study demonstrated significant reduction in RV:LV ratio, PA pressures, modified Miller scores (an index of clot burden based on angiographic assessment of obstruction), and mortality rates (2% in hospital and 3% at 30 days). There was only one death in 31 patients with massive PE.[12] There were no intracranial hemorrhages and complication rates were lower, with GUSTO (Global Utilization Of Streptokinase And Tpa For Occluded Arteries) bleeding rates of 0.7% severe and 10.7% moderate at 30 days. Of the 17 observed bleeds, 6 patients were

known to have significant bleeding co-morbidities before the procedure.[12]

B. ANGIOVAC—A LESS INVASIVE EMBOLECTOMY

The Angiovac device (AngioDynamics; Latham, NY) is a 22 Fr. cannula that has a balloon actuated funnel tip that can further expand the aspiration area, and utilizes an extracorporeal centrifugal pump to aspirate, filter, and re-infuse large volumes of blood for the removal of fresh clot or emboli. In addition to its FDA approved use for PE, it has also been used off-label to aspirate cardiac tumors, renal cell cancers, and endocarditis vegetations. It requires the use of a hybrid operating room with anesthesia support, as well as perfusionists to manage the pump/bypass circuitry. It can be used in lieu of surgical embolectomy for large volume iliac and IVC clots as well as intra-cardiac thrombus and pulmonary emboli. Because it can rapidly remove obstructive or threatening thrombi, it may represent an alternative approach in patients with significant contraindications to clot lysis, hemodynamic instability that precludes lengthier infusion therapy, and/or clinical factors that pose a high risk for surgical embolectomy.

PERT—BRINGING COORDINATED RESOURCES TO BEAR CONSISTENTLY

The idea of a multi-disciplinary pulmonary embolism response team was first introduced by Massachusetts General Hospital (MGH) in a publication in Chest in November, 2013. While still in its conceptual infancy, the idea has rapidly gained traction nationally. Lancaster General Hospital is one of the initial collaborators in a PERT consortium launched by MGH of similarly minded institutions that are now developing these teams and sharing data. The design of our PERT program was a multi-disciplinary collaboration of physicians from pulmonary and emergency medicine, interventional radiology, interventional cardiology, and cardiothoracic surgery, with further support required from anesthesia, perfusion, and imaging services.

The overall goal of initiating this program was to improve outcomes in PE patients by providing a mechanism for rapid assessment of suspected or confirmed sub-massive or massive PE, with quick acquisition and review of pertinent history and data to determine a most appropriate individualized approach to each case. Initial PERT roll out has begun in the LGH Emergency Department as the most likely point of identification of the majority of these high risk PE patients. The eventual goal is to offer this protocol hospital-wide, and as a potential community resource for patients transferred from other institutions.

THE PERT PROTOCOL

Initial activation of the PERT protocol begins in the Emergency Department with the identification of a suspected or confirmed sub-massive or massive PE. Activation includes stat diagnostic studies focused on evaluation of RV function/impairment including STAT echocardiography if RV:LV is not already well defined by other studies such as computerized tomographic pulmonary angiography. Activation also starts the consultative process, with the primary responder being the pulmonary/critical care services. They coordinate further clinical evaluation if the diagnosis is not clear and/or to eliminate minor PE. If the diagnosis is confirmed, the optimal treatment modality such as lytic therapy is clear and there are no contraindications, therapy is initiated and the protocol is completed. (Examples of contraindications include medical co-morbidities, a patient who requests palliative therapy only, or a minor pulmonary embolism that would not benefit from more aggressive therapy.)

In cases where the optimal management is not clear, or it appears the patient would definitely benefit from a procedural approach, a second tier is activated from a call pool of interventional cardiology and interventional radiology, which includes the covering cardiothoracic surgeon and an invasive angiographer. Bedside discussions are held with the consultants and the activating physician to work toward a consensus approach to management. If EKOS is chosen as the treatment modality, the patient is transferred urgently to the Interventional Vascular Unit for intervention and is then admitted post procedure to the intensive care unit on the critical care service. If the Angiovac device is employed, the patient is transferred to the hybrid operating room with the activation and support of anesthesia, perfusion services, and cardiothoracic surgery as primary operators. Post procedure these patients are also admitted to the intensive care unit. All episodes of activation are included in our institutional registry for future retrospective analysis and on-going process improvement.

THE NEXT GREAT LEAP FORWARD?

While the approaches described here are clearly in their infancy, we have great hope that the favorable

early safety data and clinical metrics observed so far are indications of the at-large 'real world' experience that will follow. Efforts like the PERT consortium may prove critical to the refinement and eventual success or failure of this approach. If the improvements in outcome seen at this early stage are sustained, and newer therapies are thoughtfully and appropriately applied, the future may be much brighter for pulmonary embolism. Practitioners may no longer be trapped between the historic limitations of aggressive therapy and the unsatisfying outcomes of conservative therapy.

The applications of new approaches will only be as successful as our ability to identify the patients at greatest risk of a poor outcome. Our growing insight into the clinical markers critical to risk stratification, combined with a focus on multi-disciplinary evaluation and individualized treatment, has the potential to bring about a significant shift in the management of this important clinical entity.

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Todd Wood, MD RPVI
Medical Director LGH Vascular Institute
Interventional Cardiology & Vascular Medicine
The Heart Group of Lancaster General Health
217 Harrisburg Ave. Lancaster, PA 17603
717-544-3800
twood2@lghealth.org