EDITORIAL

2023 Dr. Pedro Cossio Foundation Award

Premio Fundación Dr. Pedro Cossio 2023

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The 49th Argentine Congress of Cardiology was held with its usual success from October 19 to 21, 2023. The Scientific Committee of the Congress selected 4 works to contend for the 2023 Dr. Pedro Cossio Foundation Award. The winning work was:

Initial Diuretic Efficiency as Predictor of Diuretic Resistance and Clinical Outcome in Acute Decompensated Heart Failure.

Cristhian Scatularo, Luciano Battioni, Analia Guazzone, Guillermina Esperón, L. Corsico, Pablo Alcantara Costas, Hugo Grancelli

Acute decompensated heart failure (ADHF) is one of the most common causes of hospital admissions in the coronary care unit. It is usually defined as the new onset or worsening of symptoms or signs of congestion or systemic hypoperfusion. Early diagnosis and timely treatment are needed to prevent the high mortality associated with delayed treatment of this serious clinical condition. Loop diuretics are the cornerstone for achieving adequate decongestion and restoring clinical stability. The guidelines of the European Society of Cardiology (1) and the Consensus Statement on Heart Failure of the SAC (2) recommend the use of these drugs (class I), based on level of evidence C (experts opinion). This level of evidence is due to the limited evidence on mortality reduction with diuretics. The recently published ADVOR study suggests the benefit of adding acetazolamide, a carbonic anhydrase inhibitor, to loop diuretic therapy. (3) Other additional measures include oxygen therapy, vasodilators, pressor agents, inotropic drugs, or mechanical support. The severity of ADHF is related, among other parameters, to the intensity of diuretic treatment required to compensate for it and is worse when the dose of diuretic required is higher due to diuretic resistance (DR). (4) The efficacy of diuretic treatment can be assessed by measuring the urinary output or weight loss achieved. However, these individual factors may be inadequate surrogates of therapeutic effectiveness due to the presence of associated confounding factors. For this reason, the concept of diuretic efficiency (DE) was introduced. Diuretic efficiency is calculated by dividing the urinary volume or weight loss achieved (numerator) by the dose of intravenous diuretics administered (denominator). This marker has proved to be more consistent than its individual components and could provide better prognostic information. (5) The present study is a prospective, multicenter, and open analysis including 157 patients (56% men) with a median age of 74 years. The aim of the study was to assess whether the initial DE is correlated with and can predict patients' outcomes. The authors used the following definitions: 1) DR: requirement of furosemide ≥240 mg/day during the first 72 h of hospitalization; 2) DE: ratio of net fluid balance and cumulative amount of intravenous furosemide within the first 24 h. The exclusion criteria were creatinine ≥ 2.5 mg % or being on dialysis at admission, systolic blood pressure < 90 mm Hg, cardiogenic or septic shock, initial requirement of pressor or inotropic agents, mechanical ventilation (MV) or pregnancy. After bladder evacuation, an initial intravenous bolus of 40 mg of furosemide was given to patients within two hours of admission to the emergency department. In the first 24 hours after admission, all patients received intravenous boluses of 20 mg of furosemide every 8 hours. After the first day of hospitalization, the daily furosemide dose was adjusted (increased or decreased) every 24 hours, with evaluation of the extent of clinical congestion or daily diuresis (fluid balance threshold of -2000 mL/day). According to the protocol, up-titration of furosemide was performed by increasing the intravenous infusion. Down-titration of furosemide in the protocol allowed for shifting from intravenous to oral administration upon achieving an adequate response. The diuretic protocol was discontinued 72 h after enrollment or earlier in case of requirement of doses of furosemide ≥240 mg/day, tubular diuretic blockade (TDB), hypertonic saline (HS), renal replacement therapy (RRT),

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President of the Jury

inotropic drugs, pressor agents, or MV. The composite end point (CEP) was in-hospital mortality, readmissions for ADHF at 60 days or cardiovascular mortality at 60 days. Diabetes was present in 36%, atrial fibrillation in 43% and chronic kidney disease (CKD) in 20%. The etiologies were ischemic heart disease in 27%, valvular heart disease in 22%, and hypertension in 15%. Left ventricular ejection fraction (LVEF) was reduced in 43%, mildly reduced in 12% and preserved in 45%. The initial DE was -15 mL/mg (IQR -20 to -11) and there were no differences in DE across the entire spectrum of LVEF or between the different clinical types of ADHF. Diuretic resistance occurred in 13%. Worse DE value predicted the development of DR (OR 1.072; 95 % CI 1.015-1.130; p = 0.013). Patients with DE above -11 mL/mg were highly unlikely to develop DR [area under curve (AUC) 0.73; negative predictive value (NPV) 92.5% and positive predictive value (PPV) 30%]. Worsening renal function occurred in 22% of patients. Worse DE value was associated with a trend towards higher use of TDB (p = 0.07) and RRT (p = 0.06). Worse DE value was associated with the CEP (p = 0.025), mainly due to higher in-hospital cardiovascular mortality (OR 1.2; 95% CI 1.06-1.36; p = 0.0013), persistent congestion at 48 hours (p = 0.007), higher cumulative dose of furosemide at 72 h (p = 0.001) and worsening ADHF during hospitalization (p = 0.004). Cardiovascular mortality during hospitalization and at 60 days was 5.7 % and 6 %, respectively, and readmission rate due to ADHF at 60 days was 12%. In summary, the formula described above provides a simple, effective, and pragmatic method for measuring DE. This method can help identify cases of ADHF with a worse prognosis, allowing for more intensive diuretic treatment or other pharmacological or non-pharmacological therapeutic measures. This study contributes to the limited literature available on the vital benefits of diuretics in ADHF. Knowledge of the diagnostic tool described above would likely increase with greater and longer experiences.

The other candidates for the Cossio Award were:

Temporal Variability in Lp(a): Should we Repeat Testing?

María G. Matta, Laura Schreier, Augusto Lavalle-Cobo, Sebastián Garcia-Zamora, Agustina Ferraresi, Ángeles Madsen, Sofia Bellini, Guadalupe Ramos, Paula Roubicek, Pablo Corral.

Lipoprotein (a) or Lp(a), first described by the Norwegian Kar Berg in 1963, (6) consists of one molecule of cholesterol-rich LDL particle attached to one molecule of apolipoprotein(a) via a disulfide bond. Apolipoprotein(a) possesses structural homology with plasminogen, causing competitive inhibition of fibrinolysis. Thus, Lp(a) has prothrombotic and antifibrinolytic effects. In addition, Lp(a) can easily cross the endothelium and contribute to the development and growth of atherosclerotic plaques. It also increases the expression of pro-inflammatory cytokines and interleukines. This triple mechanism (proatherogenic, prothrombotic and proinflammatory) makes Lp(a) a novel risk factor for atherosclerotic cardiovascular disease that it is not considered in the different risk scores known. Elevated Lp(a) levels are strong independent predictors of myocardial infarction, aortic stenosis, heart failure, stroke, peripheral artery disease and cardiovascular mortality. (7) Its presence is genetically determined , with a strong familial tendency, and about 40 isoforms and several polymorphisms can be expressed. Additionally, there is a clear continuous association between Lp(a) concentration and the severity of each affection. (8) This association may vary according to ethnicity, diet, thyroid function, menopause, pregnancy, renal failure or inflammation. (8) In 80% of individuals, plasma Lp(a) levels are less than 70 nmol/L, and cardiovascular risk increases gradually beyond this limit. Plasma levels increase with statins while PSCK9 inhibitors decrease them. Currently, there is no treatment available to reduce Lp(a), but there are several ongoing phase I-II studies with antisense oligonucleotides and small mRNA. The European Atherosclerosis Society Consensus Statement on Lp(a) (8) and the SAC Consensus Statement on Cardiovascular Prevention (9) recommend universal measurement of plasma Lp(a) "at least once in a lifetime" (class I, level of evidence C). The aim of the authors of the work commented was to analyze the possible variability of Lp(a) over time in clinically stable patients. The secondary objective was to evaluate the causes of this variability. They conducted a prospective analysis of 740 Caucasian patients attending a lipid clinic from February 2018 to December 2022. For this investigation, they included 61 of these patients with at least two Lp(a) determinations taken within a minimum interval of 4 months. This interval was chosen empirically due to lack of evidence regarding measurement intervals. Normal values were defined as those below 70 nmol/L, borderline values as those between 70 and 125 nmol/L, and elevated values as those above 125 nmol/L. Mean age was 59.6 ± 13.0 years and 62.3% were men. Lp(a) variability was estimated by calculating the percentage change between the reference value and the measured value with the largest discrepancy. Forty-three percent of participants had Lp(a) > 70 nmol/L, less than 20% had a history of cardiovascular disease, and most were treated with statins. The study analyzed 171 determinations from 61 participants, ranging from a minimum of 4 months to a maximum of 48 months. Thirty-four participants had 2 determinations, thirteen had 3, eight had 4, five had 5 and one had up to 7. Twenty-one of the 61 participants (34.4 %) showed a variability ≥ 25 %. Five patients (38.46 %) were in the Lp(a) category < 70 nmol/L, 6 (54.54 %) were in the borderline Lp(a) range and 10 (27.02 %) were in the high Lp(a) category. Two patients in the lowest

category moved to a higher category, two in the borderline category moved to the highest category and one moved to the lowest category, and two of the 10 patients in the highest category moved to the borderline category. Thus, 7 (11.45%) participants moved to another category. One possible cause of these variations could be an increase in Lp(a) due to the initiation of statin treatment, discontinuation of PCSK9 inhibitors, or transition to menopause. The possibility of variations in LP(a) concentrations over time was suggested in a sub-study of the ARIC (Atherosclerosis Risk In Communities) program which demonstrated that patients with borderline high Lp(a) concentrations may have changes ≥ 20 nmol/dL over time, particularly if they are black, women, or have diabetes or hypertension. (10) Recently, Gaba et al. reported the results of the OCEAN(a)-DOSE study. In this phase 2, randomized trial of the Lp(a)-lowering small interfering RNA (siRNA) therapy olpasiran in 281 patients with atherosclerotic cardiovascular disease and Lp(a) >150 nmol/L, 51% of patients in the placebo arm experienced an upward or downward ≥ 50 nmol/dL change on repeated sessions. (11) These observations challenge the recommendations of guidelines and consensus statements, (8,9) in line with the paper being analyzed. Future studies should confirm or rule out this hypothesis. As a final comment, the recommendation to perform the measurement at least once is unclear. Only once? How many times? The answer is probably to repeat testing in borderline cases to determine whether there is a shift to the higher or lower category. It is yet to be determined whether these variations have any impact on the subsequent incidence of clinical events.

Novel Variables in Cardiopulmonary Exercise Testing with Additional Prognostic Value in Different Subtypes of Pulmonary Arterial Hypertension

Raul Ignacio Pasetto, Jorge Kriskovich, Celeste Lopez, María Lorena Coronel, Jorge Franchella

The use cardiopulmonary exercise stress test (CPET) provides some typical findings in patients with pulmonary hypertension (PH): low end-tidal carbon dioxide partial pressure ($ETPCO^2$), high ventilatory equivalent for carbon dioxide (VE/VCO^2), low oxygen pulse (VO^2/HR), and low peak oxygen consumption (peak VO^2). (12) A recent study conducted in our country, selected to receive the SAC Cossio Award in 2022, suggests that CPET could be used to reclassify patients with PH who are considered to be at low risk. In other words, to establish "high risk of low risk". (13) The aim of the study here analyzed was to establish the prognostic ability and cut-off points for new variables such as circulatory power (CP), (14) defined as the product of peak VO^2 by the peak systolic blood pressure reached during exercise, and ventilatory power (VP), calculated as the peak systolic blood pressure reached at peak exercise divided by VE/VCO^2 (peak SBP /VE/VCO^2). (15) It was carried out at Instituto de Cardiología de Corrientes and included 14 male patients with a mean age of 36 ± 14 years followed up for an average of 790 days. Seven patients had PH associated with congenital heart defects (4 with atrial septal defect and Eisenmenger's syndrome, one with tricuspid atresia, Fontan surgery and Eisenmenger's syndrome, 2 with pulmonic stenosis and one with tetralogy of Fallot). Six patients had idiopathic pulmonary arterial hypertension, and one had PH associated with connective tissue disease (systemic lupus erythematosus). On admission, 4 patients were in functional class (FC) I, 10 in FC II and none in FC III or IV. The primary end point was a composite of death, worsening FC or in-hospital admission for worsening PH. Four patients worsened their functional class, one of them had to be hospitalized, and there were no deaths. The mean duration of the CPET was 10.37 minutes, and the mean values of the variables were: peak VO^2 18.69 mL/kg/minute (49.15% of predicted peak VO^2); VE/VCO^2 47.96; VP 2.57 and CP 1902. The variables that demonstrated prognostic ability and their corresponding cut-off points are as follows: VE/VCO^2 42.5 (with a sensitivity of 75%, specificity of 66%, and an area under the curve of 0.8), peak $VO^2$15.35 mL/kg/min (with a sensitivity of 75%, specificity of 70%, and an area under the curve of 0.65), VP 2.3 (with a sensitivity of 75%, specificity of 78%, and an area under the curve of 0.77), and CP 1730 (with a sensitivity of 100%, specificity of 66%, and an area under the curve of 0.66). After multivariate analysis, PC still had the ability to predict the endpoint. This study adds novel information about the usefulness of CPET in PH. However, due to the limited number of patients included and the heterogeneity of the sample, it should be considered an exploratory investigation.

Do Patients with Pulmonary Embolism Associated with Active Cancer and Moderate or Severe Risk Score have Higher Risk of Adverse Outcome than Those Without Cancer?

José M. Bonorino, Jorge A. Bilbao, Nicolás A. Torres, Mateo Iwanowski, Emilia M. Spaini, Agustina F. Gallegos, José C. Santucci, Renzo Melchiori, María E. Aris Cancela, Horacio E. Fernández.

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) or pulmonary embolism (PE), is the third leading vascular disease after myocardial infarction and stroke. Its incidence increases with age as is almost eight times more common in subjects > 80 years than in those in their fifth decade of life. (16) The frequent association of cardiovascular diseases with cancer (the two leading causes of death in our environment) gave rise to the development of a new sub-specialty: cardio-oncology. (17) The association between cancer and PE was first recognized over a century ago by Armand Trousseau. (18) The incidence of PE in the general population is 0.1%, but

it is much more common in cancer patients, with a prevalence ranging from 2-15%. (19) This is especially true for metastatic tumors and is related to the type and primary location of the tumor (adenocarcinomas of the gastrointestinal tract, kidney, ovary, malignant brain tumors, and hematologic neoplasms), cancer staging, and antineoplastic treatment (chemotherapy, radiotherapy, and postoperatively). (20) The clinical presentation of PE varies widely, from mild cases that can be managed on an outpatient basis with a favorable outcome, to highly complicated cases with a high mortality rate. Several models have been described to quantify its severity and prognosis. The Pulmonary Embolism Severity Index (PESI) is one of the most extensively validated clinical scores. It is made up of 11 clinical variables with their corresponding scores. The scoring system categorizes patients into five classes based on their score. Class I (score < 65 points) has a mortality rate of less than 1.5%, while class V (score > 125 points) has a mortality rate between 10% and 25%. (21) The authors of this paper asked whether patients with PE and a moderate or severe PESI index (≥ 86 points) and active cancer have a worse outcome compared to those without cancer. For this reason, they conducted a single-center, retrospective and descriptive analysis of a prospective cohort attending Hospital Universitario Austral. Of 456 patients hospitalized between 2008 and 2022 with a diagnosis of PE, 209 had a PESI score ≥ 86. The study compared the incidence of in-hospital mortality (IHM), use of pressor agents (PA), and need for mechanical ventilation (VM) in patients with PE with and without cancer. Active cancer was defined as solid or hematological malignancies that have received chemotherapy and/or radiation treatment within the last year, or those without active treatment who are receiving palliative care. The population with PE and cancer was younger than the one without cancer (65 vs. 70 years, $p < 0.05$). The prevalence of hypertension was lower in patients with cancer (48% vs. 72%, $p < 0.05$) but the prevalence of diabetes was higher (19% vs. 8%, $p < 0.05$), respectively. A PESI score ≥ 86 was more frequent in patients with PE and cancer (100% vs. 84%, $p < 0.05$). There were no differences in IHM between both groups (12.7% vs. 8%, p = NS); however, the use of MV and PA was lower in patients with PE and cancer (9% vs. 34%, $p < 0.05$, and 11 % vs. 23%; $p < 0.05$, respectively). There were no deaths among patients with cancer (n = 24) or without cancer (n = 151) and PESI score < 86 points. In patients with cancer, PESI score < 86 vs. ≥ 86 points was not useful to predict IHM (0% vs. 12%, p = NS). The authors conclude that patients with PE and cancer and intermediate or high PESI scores are not at an increased risk of an unfavorable outcome. Mortality rate was not higher in this group and the need for MV and PA was lower. The small sample size likely contributed to the lack of statistical significance in the observed differences, as the trends exhibit wide variability. Several publications suggest different results. For example, Sorensen et al. analyzed 668 patients with PE and cancer from a Danish registry and reported 38% survival at one year in patients with cancer vs. 47% in the control group (RR 1.35, 95% CI 1.20 -1.50; $p < 0.001$). (22) Researchers from the University of Padua concluded that the presence of cancer significantly increases the risk of recurrent PE with poor vital prognosis (HR 1.72, 95% CI 1.31- 2.25]. (23) Recently, Rapezzi et al. published a study analyzing clinical trials with neutral or negative results. These situations suggest the possibility of a higher rate of total events than actually observed, smaller differences in the number of events between groups than calculated, or shorter follow-up periods than necessary. (24)

The jury of the 2023 Dr. Pedro Cossio Foundation Award was formed by the former presidents of the Argentine Society of Cardiology, Dr. Ana María Salvati and Dr. Ricardo Migliore, to whom I am grateful for their skilled and responsible participation.

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