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EDITORIAL

Medicine & Science Journal: a new multidisciplinary journal to fill the knowledge gaps in medical sciences through preclinical and clinical evidence

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The just started year 2023 is going to leave behind a long period ruled by the COVID-19 pandemics, that has deeply affected our lives and caused important development slowdowns in many aspects of science and medicine. For this, we would like to celebrate the beginning of this year of scientific renaissance by welcoming the "Medicine & Science Journal" (MSJ) published by Clinical Network Digital Medical Publisher [1]. A special appreciation goes to the International Editorial Board, for the impressive effort in establishing a new miliary stone in the era of modern medicine with this new scientific journal encompassing both experimental and clinical science in a fully translational package. The MSJ is a free open access journal for the public to read, aiming to achieve soon indexing in Scopus and Medline [2].

As Plato stated "…The beginning is the most important part of any work, especially in the case of a young and tender thing; for that is the time at which the character is being formed and the desired impression is more readily taken" [3]. For this we encourage junior and senior clinicians and researchers to consider this just born multidisciplinary publishing option. The MSJ is a broad-spectrum scientific journal including different aspects of medical science. The main thematic areas include, but are not limited to, Internal Medicine, Cardiology, Pneumology, Neurology, Hematology, Infectious Disease, Oncology, Pharmacology, Emergency Medicine, Anesthesiology and Intensive Care, and Preclinical and Basic Science.
In recent years, knowledge advances in therapies for several acute and chronic

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diseases and changes in practice guidelines based on novel evidence, have notably impacted on the comprehensive field of internal and emergency medicine. For instance, novel and groundbreaking therapies with promising prognostic implications have emerged for the treatment of heart failure, diabetes, respiratory failure, shocks, sepsis, and hypercholesterolemia, as well as for the management of patients needing anticoagulation for cardiovascular prevention. Similarly, acute care of patients in the pre-hospital setting or in the emergency department have changed concurrently with the continuous rising of technological innovations. Indeed, in the past decade, the healthcare systems have seen a sped up in digital transformation and technologies like never before, i.e. introduction of the artificial intelligence, telemedicine, apps and wearable monitoring systems, up to drugs and defibrillators delivered by drones. The call for personalized and precision medicine, also grounded on the advancement gained in the omics technologies and in epigenetics, has prompted research across medical and biological disciplines, largely supported by cutting-edge developments in the field of bioinformatics. The holistic field of medicine strives to spread innovative research, clinically relevant for the daily practice in general and emergency medicine and in the different medical specialties.

Thus, despite the extraordinary advances in cardiology, including innovations in medications, diagnostic modalities, and therapeutics, cardiovascular diseases remain the leading cause of morbidity and mortality globally. Cardiovascular care represents for many healthcare systems and organizations the daily battlefield where medical professionals at each level struggle against the suboptimal quality of care, inconsistent health outcomes, and unsustainable care costs. In this context, the MSJ mission is to provide clinicians with an understanding of the latest developments in cardiovascular medicine and to support and enrich their daily practice, by encouraging submission of manuscripts dealing with the precision medicine approach, exploiting the clinical, genetic, pharmacological, and biomarker information, going beyond the "classical" approach. Finally, a special place is given to digital transformation in cardiovascular health care, focusing on virtual care in heart failure, remote monitoring of cardiac arrhythmias, and artificial intelligence-driven cardiovascular care. In parallel, all aspects of the respiratory system, including physiology, pathophysiology, epidemiology, immunology and pharmacology of respiratory diseases, as well as new therapeutic interventions are covered by the respiratory section of the journal. Significant advances in precision medicine, which are likely to impact on clinical practice in pneumology are also expected.

The fast-growing field of Neurology includes multiple and often chronic disorders which have huge impact on patients' everyday life due to high epidemiologic indices and complex diagnostic and therapeutic management. In the last few years, numerous advances in genetics, laboratory testing and neuroradiology have been made leading to a better understanding of the intrinsic biological mechanisms behind neurological diseases, i.e.: identification of rare and unknown gene mutations in patients suffering from epilepsy; discovery of specific blood biomarkers for the diagnosis of neurocognitive disorders; the spreading use of perfusion-CT in acute cerebrovascular ischemic events; the use of monoclonal antibodies in the field of migraine. Translation from mechanisms to clinical practice is fundamental to guarantee the best clinical patient care.

Hematology is a specialty covering both clinical and laboratory aspects of adult and pediatric diseases, either malignant or non-malignant. Over the last years a great number of investigations have been made in diagnostic and therapeutic areas, contributing to the advancement of this discipline. Thus, an increasing understanding of molecular aberrations that trigger the development of leukemias has been reported, while a growing use of novel molecular biology technologies advanced the development of investigational drugs targeting driver genetic mutations. Immune-targeted therapies, including monoclonal antibodies targeting B cell-and T-cell associated antigens, tyrosine kinase inhibitors, bispecific antibodies and chimeric antigen receptor T- cell therapy, represent other attractive area of investigation. Finally, a rapid progress in stem cell research has paved the way for the development and use of new cell therapy products in regenerative medicine with several applications in hematology, transfusion medicine, and rheumatology/neurology fields related to transplantation. Similarly, the therapeutic scenario in Oncology has rapidly evolved with the introduction of several new drugs including targeted therapy, immune

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checkpoint inhibitors and/or their combination. The better understanding of biological and molecular mechanisms underlying tumor growth and progression as well as resistance to treatments has drastically revolutionized the therapeutic treatment algorithms of main solid tumors. A new era is starting with a considerable overcrowding in the therapeutic landscape, raising many questions that need to be addressed.

As we have unfortunately experienced, increasing human mobility due to international tourism, work, study and migration is a key factor for microorganism circulation worldwide. The cost of this increased mobility is the threat of a possible spread of known diseases with a significant epidemic potential and of newly identified or unidentified ("X disease") pathogens associated with a strong pandemic risk. Given that disease spreading is a considerable danger, we should not underestimate the main emerging infectious diseases presenting high epidemic potential. Additionally, infections are becoming a major threat for hospitalized patients, often fragile and immunosuppressed. Enhancing the basic infectious disease research for the development of immunotherapies, advanced diagnostics, vaccines, antimicrobial therapies effective in cases of infections by multidrug-resistant agents or other treatments capable of strengthening or restoring the immune defenses is therefore of fundamental relevance. The MSJ welcomes studies focusing on epidemiology, pathogenesis, immunology, and pharmacology about bacterial, viral, fungal and parasitic diseases, as well as preventive medicine protocols, public health policies and new emerging treatments.

The Pharmacology section represents the common thread among the different topics covered by MSJ, together with the area of emergency medicine and critical care medicine which cover the medical aspects related to the most acute patients and those treated in intensive care, requiring multiple organ function supports and advanced tools for prognostication.

Finally, preclinical research represents a key step in studying the potential of new drugs or therapeutic strategies before their translation into clinical trials. Current development in in vitro, in vivo and in silico experimental models allow for replication of biological phenomena underlying a wide range of pathologies. The preclinical and basic science section of MSJ covers a broad area of research, including all the clinical topics above discussed, i.e. internal and emergency medicine, neurosciences, physiology, cardiovascular medicine, pharmacology, hematology, oncology, infection disease, anesthesia and critical care. Basic science represents a leading aspect of MSJ, with the ambition to spread preclinical studies designed, conducted, analyzed and reported to the highest levels of rigor and transparency.

Socrates may ask if "…is it true; is it kind, or is it necessary?" …to have a new journal [4]? The answer is yes! Indeed, the MSJ is born with the aim to represent a new dynamic entity making a link from bench to bedside, from laboratory experiments through clinical trials to point-of-care applications, with a privileged perspective towards inclusiveness and interdisciplinarity. The MSJ is not just a new journal but the journal that will stimulate further advancement in the most emerging research topics, for continuing education of the medical community and the best delivery of care to patients. We are grateful to researchers, international scientists, clinicians, and academicians for their personal and successful contributions to promote a cultural challenge toward a new horizon in medicine and science, improving multidisciplinary and multiprofessional collaboration in basic sciences and clinical trials [5].

Publisher's Note

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CASE REPORT

Right Ventricular Failure in a Patient Supported with VV-ECMO: Implications and Therapeutic Strategies

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Keywords: Veno-venous extra corporeal membrane oxygenation; acute respiratory distress syndrome; right ventricular failure; right ventricular assist device, right ventricle.

Abstract

A 46-year-old woman was admitted to the intensive care unit with severe acute respiratory distress syndrome (ARDS) due to Legionella pneumonia. Refractory hypoxemia developed despite conventional lung-protective mechanical ventilation and the patient was managed with veno-venous extracorporeal membrane oxygenation. Subsequent right ventricular (RV) failure developed and was successfully treated with a percutaneously inserted right ventricular assist device attached to an oxygenator. This report discusses the pathophysiology, diagnosis, and treatment of RV failure as a complication of ARDS in the context of the current literature and provides a rationale for the use of mechanical circulatory support devices in this setting.

Introduction

RV dysfunction complicates 22-50% of acute respiratory distress syndrome (ARDS) cases and contributes to increased mortality [1]. Treatment with veno-venous extracorporeal membrane oxygenation (VV-ECMO) has been shown to improve pulmonary hemodynamics [2,3] and a large randomized controlled study of ARDS patients demonstrated that duration of vasopressor use was shorter in the VV-ECMO group [4]. As VV-ECMO therapy alone does

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not directly unload the right ventricle (RV), a right ventricular support device that is coupled to an oxygenator and can bypass the RV may be beneficial in cases where severe RV dysfunction complicates ARDS. In this report, a case is presented and used to discuss the pathophysiology, diagnosis, and treatment of RV failure as a complication of ARDS in the context of the current literature and presents a clinical algorithm to guide the use of mechanical circulatory support devices in this setting.

Case Report

A 46-year-old woman with a past medical history significant for scleroderma-related interstitial lung disease was transferred to an ECMO-capable intensive care unit (ICU) with a diagnosis of Legionella pneumonia. She was not known for prior cardiovascular disease and her most recent estimated systolic pulmonary artery pressure (PAP) by transthoracic echocardiography, a year prior, was 34 mmHg.

On the day of her transfer, she was intubated due to worsening hypoxemia. Despite optimization of conventional mechanical ventilation her oxygen saturation (SpO_2) remained below 80%. Upon arrival, the PaO_2/FiO_2 ratio was 86 mmHg while paralyzed and ventilated with a pressure-controlled setting targeting a tidal volume of 6 ml/kg predicted body weight with a positive end-expiratory pressure (PEEP) of 10 cmH_2O and a fraction of inspired oxygen of 1. Due to refractory hypoxemia from Legionella related ARDS and the rapidity of deterioration, VV-ECMO support was implemented. A 31 Fr double-lumen Avalon catheter (Getinge, Gothenburg, Sweden) was inserted via the right internal jugular vein. The patient suffered a cardiac arrest necessitating extracorporeal cardiopulmonary resuscitation (eCPR). A 19 Fr arterial return cannula was advanced into the left femoral artery for veno-arterial (VA-ECMO) support and a 21 Fr venous cannula was placed in the right femoral vein for additional drainage. Return of spontaneous circulation was achieved within 10 minutes after her oxygenation improved with extracorporeal support.

Periprocedural echocardiography after resuscitation demonstrated normal biventricular systolic function. Gradually, VA-ECMO was weaned along with vasopressors resulting in conversion to VV-ECMO 32 hours later. Due to the extensive pneumonia and severe intrapulmonary shunting, oxygenation was persistently poor, requiring VV-ECMO flows up to 5.4 L/min to maintain a PaO_2 above 70 mmHg. A target PCO_2 of < 40 mmHg was maintained with a sweep gas flow of 8 L/min.

After 150 hours of VV-ECMO support, her mean arterial pressure decreased < 60 mmHg that was treated with a norepinephrine infusion. Concomitantly, the central venous pressure (CVP) rose to 20 mmHg and metabolic acidosis with high lactate developed. Transesophageal echocardiography revealed a dilated, severely hypokinetic RV whereas the LV was small with a normal systolic function. A decision was made to replace the existing Avalon double lumen cannula with a Protek Duo cannula (TandemLife, Pittsburgh, PA, USA) in series with an oxygenator. Increased intravascular volume was treated with diuretics while milrinone, inhaled nitric oxide (iNO) and sildenafil were utilized to address increased pulmonary vascular resistance (PVR). Gradually the blood pressure and lactate improved, and vasoactive agents were discontinued. Oxygenation and ventilation also improved leading to cessation of iNO after 4 days and milrinone after 9 days. Blood flow and sweep gas were slowly waned and ECMO support was stopped 16 days after the catheter change. The patient was transferred to her community hospital for further rehabilitation one month later. A summary of the patient's ventilatory, hemodynamic, and ECMO parameters over the course of hospitalization is presented in **Table 1**.

Table 1 - Details of hemodynamics and respiratory measurements 1/2

	ECMO				Respiratory Support				Hemodynamics					Arterial Blood Gas		
	Mode	ECBF	SGF	FdO_2	Mode	PIP	PEEP	FiO_2 Vent	CVP	SBP	DBP	MAP	HR	SpO_2	PaO_2	$PaCO_2$
Day 0	VA	4.16	5	1	PC	26	10	0.7	15	113	65	81	80	85%	60.6	45
Day 1		5.35	7	0.65		21	15	0.4	17	114	70	85	81	97%	69.9	35

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Table 1 - Details of hemodynamics and respiratory measurements 2/2

	ECMO				Respiratory Support				Hemodynamics					Arterial Blood Gas		
	Mode	ECBF	SGF	FdO_2	Mode	PIP	PEEP	FiO_2 Vent	CVP	SBP	DBP	MAP	HR	SpO_2	PaO_2	$PaCOO_2$
Day 2	VV	5.3	5	0.8	PC	22	15	0.4	19	106	67	80	91	99%	135	37
Day 3		5.4	5	0.7	HFNC	22	15	0.4	6	121	69	86	104	100%	146	33
Day 4		3.3	3.75	0.65		22	15	0.4	10	126	76	93	96	95%	70	38
Day 5		3.7	4	0.8		22	15	0.7	10	143	81	102	91	95%	75	45
Day 6		5.48	8	100		22	15	0.7	3	108	63	78	116	93%	75.9	41
Day 7	ProTek Duo	5.42	8	100		22	15	0.5	9	112	61	78	96	91%	61.2	35.6
Day 8		4.39	4	0.8	CPAP	15	15	0.3	14	108	68	81	68	100%	184	33.1
Day 9		4.64	5	0.8		14	15	0.3	15	108	66	80	115	99.4	134	36.7
Day 10		4.48	6.5	0.8		20	20	0.3	12	103	56	72	83	99.9	146	38.6
Day 11		4	2.5	0.6		24	20	0.3	6	107	58	74	69	93.9	71.5	61.4
Day 12		4.5	3.5	0.8	PSV	31	15	0.6	12	81	51	61	58	100	180	45
Day 13		4.57	4.5	0.6		32	20	0.5	12	117	58	78	88	99.1	98.5	48.7
Day 14		4.43	3	0.6		30	12	0.5	6	98	58	71	119	92	58	64
Day 15		4.38	3.5	0.5		30	12	0.6	8	127	64	85	74	97.9	79	49
Day 16		3.8	3.5	0.6		30	12	0.5	8	148	66	93	93	96	65	46
Day 17		3.75	5	0.7		31	12	0.5	NA	112	53	73	97	97.9	93.5	36.2
Day 18		3.63	5	0.7		30	12	0.5	NA	114	54	74	96	99	86.7	35.7
Day 19		3.16	5	0.7		30	12	0.5	NA	103	57	72	100	94.7	59.9	37.9
Day 20		2.99	5	0.7		29	12	0.5	NA	114	55	75	102	98.8	91.5	36.5
Day 21		2.74	3	0.4		29	12	0.5	NA	115	59	78	109	99.7	128	36.9
Day 22		2.78	5	0.3		30	12	0.5	NA	138	70	93	101	94	63	26
Day 23	Decannulation	2.63	0	0.21		22	10	0.5	13	113	57	76	116	98.3	90	47

Abbreviations:

ECMO = extracorporeal membrane oxygenation, ECBF = extracorporeal membrane oxygenation blood flow, SGF = sweep gas flow, FdO_2 = fraction of delivered oxygen (through ECMO circuit), PIP = peak inspiratory pressure, PEEP = positive end-expiratory pressure, FiO_2 = fraction of inspired oxygen, CVP = central venous pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, HR = heart rate, VA = veno-arterial ECMO, VV = veno-venous ECMO, PC = pressure control, HFNC = high flow nasal cannula, CPAP = continuous positive airway pressure, PSV = pressure support ventilation.

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Comment

In patients with severe ARDS, hemodynamic instability is frequently attributed to septic shock. However, many patients develop hemodynamic collapse secondary to right ventricular (RV) dysfunction and/or limitation secondary to increased intravascular volume and RV afterload [5]. Based on her medical history of interstitial lung disease, this patient had risk factors for pulmonary hypertension and RV dysfunction and the development of severe ARDS further contributed to hemodynamic deterioration [1].

Patients with ARDS are at risk for the development of RV dysfunction due to a variety of mechanisms primarily altering PVR and resulting in increased RV afterload. At the level of the pulmonary arterioles, hypoxemia and hypercapnia contribute to vasoconstriction. In addition, inflammation, microvascular thrombosis and activation of endothelial cells result in intravascular occlusion, further increasing PVR [6]. Finally, extrinsic compression of the pulmonary vasculature may occur due to the application of increased airway and transpulmonary pressure, further afterloading the RV. When alveolar pressure exceeds pulmonary venous pressure, West zone 1 and 2 (non-zone 3) conditions are favored [7]. In non-zone 3 lung units, the down-stream pressure to RV ejection is no longer left atrial pressure, but rather alveolar pressure [7-9]. The impact of mechanical ventilation on right ventricular afterload is increased in the setting of reduced lung compliance, when transpulmonary pressures are higher (as in ARDS) or when left atrial pressure is low, as can occur during RV limitation or hypovolemia [10, 11].

RV dysfunction is the representation of an impaired end systolic pressure volume relationship and is caused by a reduction in contractility or increased in afterload [5]. Compared to the LV, the RV operates at lower pressures and is more sensitive to changes in afterload. In response to an increase in afterload, the RV will increase end-diastolic volume and dilate to maintain stroke volume [11]. The RV end-diastolic pressure volume relationship has an abrupt increase when preload is maximal. When preload is maximal, RV limitation has occurred. The clinical implication is that volume loading at that point will only increase CVP without any rise in cardiac output and any increase in afterload will result in a direct decrease in stroke volume. A combination of RV dysfunction and limitation can lead to RV failure which can be diagnosed when there are clinical signs of systemic congestion and hypoperfusion. Demonstration of an elevated CVP greater than pulmonary artery occlusion pressure with low cardiac index also supports the diagnosis of RV failure. Echocardiography is frequently utilized to evaluate RV function. Echocardiographic signs that suggest RV dysfunction/limitation include low global systolic function, paradoxical motion of the interventricular septum, and an increase in the RV end diastolic dimension to LV end diastolic dimension ratio [12].

High driving pressure, high $PaCO_2$ and low PaO_2/FiO_2 ratio are independent risk factors for right ventricular dysfunction in the setting of ARDS [13]. When these risk factors are present, serial monitoring of surrogates of RV function such as systolic PAP, CVP and echocardiographic parameters can help in early identification and management. A thorough review of this topic is provided elsewhere [5]. Medical management includes optimizing RV preload by carefully limiting fluid loading and judicious diuresis, increasing RV contractility with inotropic agents such as milrinone or dobutamine, and reducing afterload with pulmonary vasodilators and ventilation strategies that limit plateau and driving pressure [14], while aiming for normalization of blood gases [1, 11, 15, 16]. VV-ECMO may reduce the mean PAP and PVR by lowering the PCO_2 and improving oxygenation [3], but it does not directly unload the RV [2] (**Figure 1**). Conversion to a venous-arterial-venous (VAV) circuit allows for bypass of both the LV and RV but adds more risk and complexity.

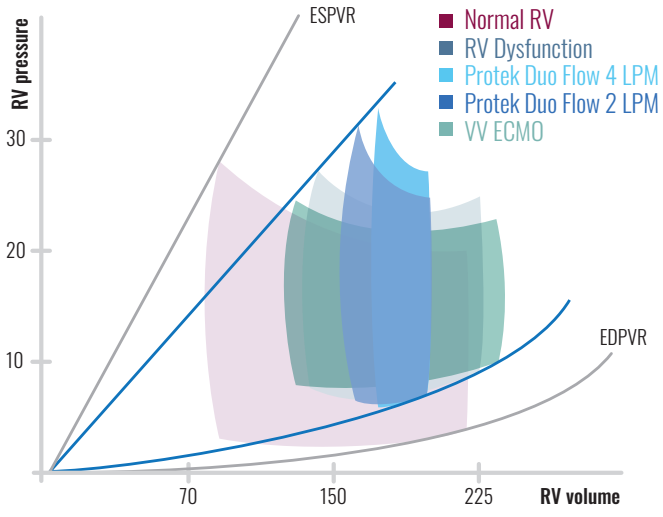

Figure 1. Pressure-volume loops of the right ventricle. The normal right ventricle is compared to right ventricular dysfunction with and without VV-ECMO and the Protek Duo device at different flows. ESPVR = end systolic pressure volume relationship; EDPVR = end diastolic pressure volume relationship.

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The TandemLife Protek Duo is a dual lumen 29 Fr catheter that can be percutaneously inserted via the right internal jugular vein (**Figure 2**).

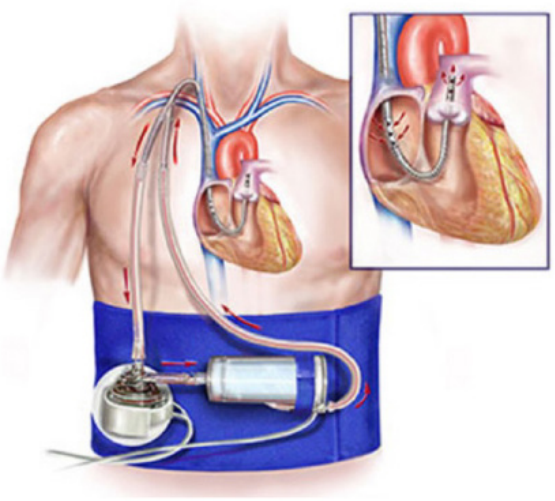

Figure 2. TandemLife Protek Duo device illustrating insertion via the right internal jugular vein into the right ventricle demonstrating bypass of blood flow from the right ventricle into the main pulmonary artery.

The proximal lumen functions as an inflow cannula and is positioned in the right atrium. The distal lumen has a multifenestrated tip and is positioned in the main pulmonary artery before the bifurcation. Blood is drained from the right atrium into the extracorporeal pump allowing flows up to 5 L/min and is returned to the main pulmonary artery via a distal lumen bypassing the RV. An oxygenator can be connected to the circuit for ECMO support to provide oxygenation and CO_2 removal, decreasing PVR and unloading the RV. The device decreases RV preload and stroke volume but also increases afterload by increasing PAP. The increase in afterload is balanced by the increase in oxygen content of the mixed venous blood and CO_2 removal provided by the oxygenator, potentially improving RV hemodynamics overall. The main disadvantage is that the cannula needs to be inserted under fluoroscopy and the single lumen configuration may limit the total flow delivered. Considering the TandemLife ProTek Duo in a situation where there is isolated RV failure will be more beneficial to the RV and less invasive than converting to a VAV circuit. A decision algorithm incorporating this device into the care of such patients is presented in **Figure 3**.

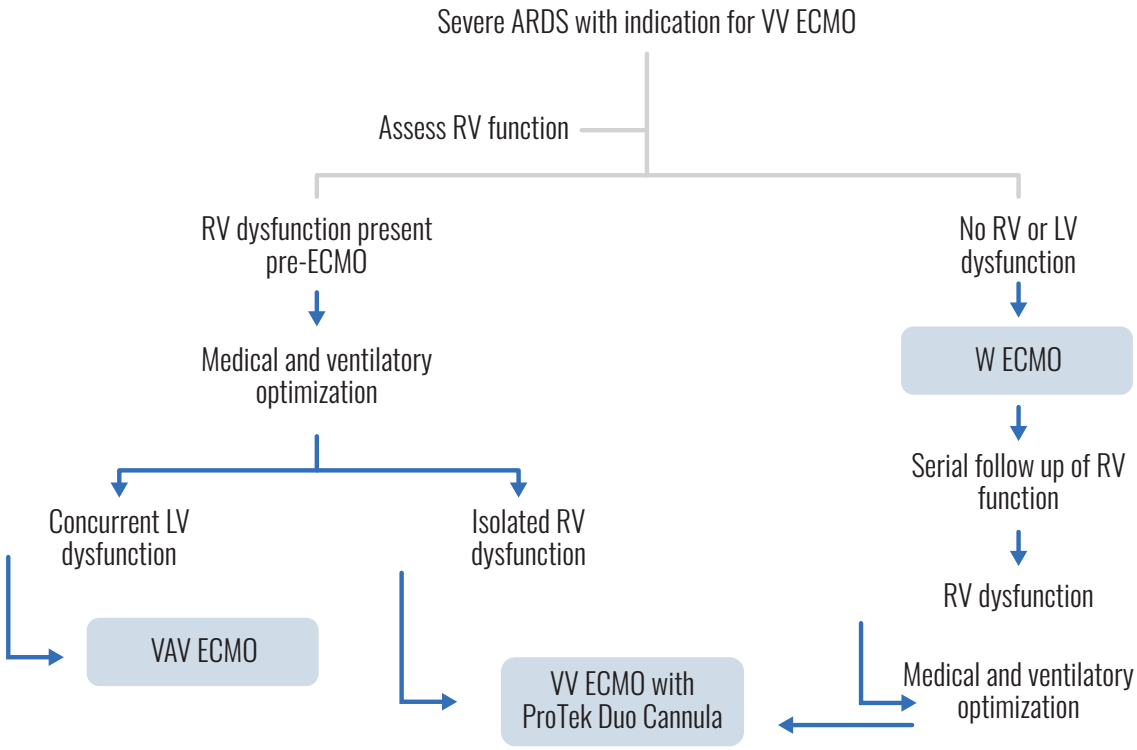

Figure 3. Decision algorithm for mechanical support of RV dysfunction in ARDS. ARDS = acute respiratory distress syndrome, VV-ECMO = veno-venous extracorporeal membrane oxygenation, RV = right ventricle, LV = left ventricle, VAV-ECMO= Veno-arterial-venous extracorporeal membrane oxygenation

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CASE REPORT

Blunt chest trauma associated with bronchial rupture and cerebral air embolism. A case report.

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Keywords: pediatric blunt chest trauma, bronchial rupture, tracheo-bronchial injuries, cerebral air embolism

Abstract

Thoracic injuries following blunt chest trauma represent a significant cause of morbidity and mortality in the pediatric population. Airway injuries, such as tracheal and bronchial rupture are quite rare with an incidence of 1-3%. We present the case of a 17-year-old girl victim of major trauma after an intentional fall from a height of 12 meters who reported subcutaneous emphysema, bilateral pulmonary contusions, a slight apical left pneumothorax and massive pneumomediastinum. Following cardio-respiratory stabilization a flexible bronchoscopy was performed. The complete avulsion of the left superior bronchus was found. Urgent thoracic surgery was performed obtaining the complete pulmonary recovery. Subsequent total body Computed Tomography (CT) control documented a large area of cortical-subcortical ischemia in the left parieto-occipital lobe. Cerebral Magnetic Resonance Imaging (MRI), performed on day 6, confirmed the findings and therefore cerebral air embolism was hypothesized. Following surgery and lung recovery patient regained consciousness and consequently discharged without any neurological or respiratory sequelae. Systemic Air Embolism (SAE) should always be suspected in case of chest trauma, especially if pneumomediastinum or pneumothorax are present and associated with neurological signs or Cerebral CT scan abnormalities. Tracheal and bronchial lesions should always be investigated and treated surgically as soon as possible in case of airway instability and/or respiratory failure.

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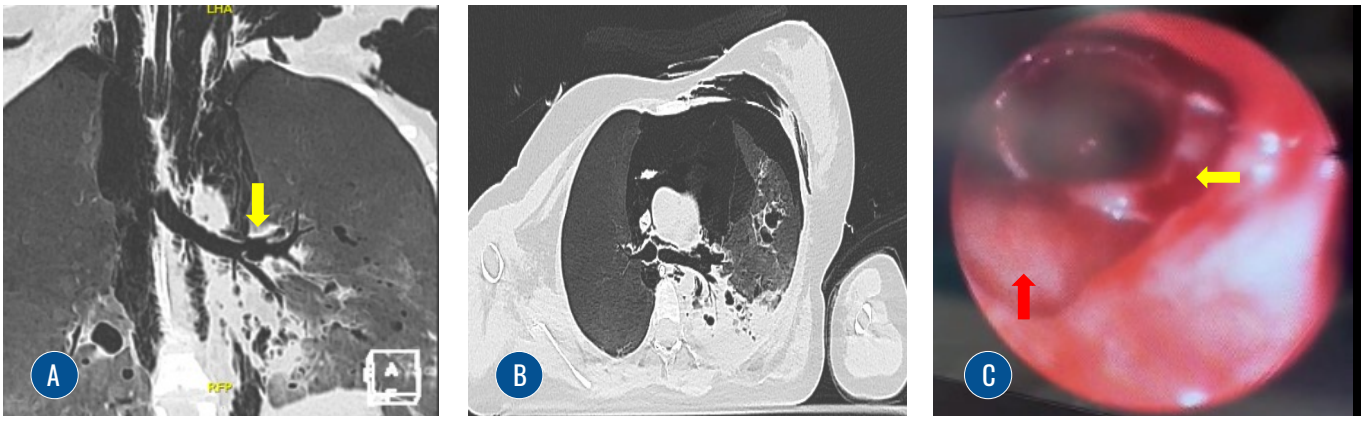
1.Introduction

Thoracic injuries following blunt chest trauma (rib fractures, lung contusion, pneumothorax and hemothorax) represent a significant cause of morbidity and mortality in the adult and in the pediatric population [1]. Airway injuries as consequence of blunt thoracic trauma, such as tracheal and bronchial rupture are quite rare. In the adult population its incidence ranges from 1 to 3% while in the pediatric population the incidence does not reach the 1%. Scientific literature regarding pediatric airway injuries after blunt chest trauma is represented mainly by reports from clinical experience probably due to the event rarity. Unfortunately, this kind of traumatic lesion is accompanied with a very high mortality rate. It is estimated that only 30% of the patients are alive at the hospital arrival [2,3]. Clinical presentation of bronchial injury may range from clear manifestations as tension pneumothorax, massive subcutaneous emphysema to less obvious manifestations as pneumomediastinum [4]. Considering its lethality, early recognition and diagnosis of traumatic tracheobronchial injuries are crucial for the patient's care and survival.

2.1 Bronchial rupture in blunt chest trauma

We present the case of a 17-year-old girl victim of major trauma after an intentional fall from a height of 12 meters. In the pre-hospital phase, patient was found with a Glasgow Coma Scale of 9 (GCS: bilateral M5V3E1) and severe cardio-respiratory instability (Blood pressure <80/50; Heart rate >150, Oxygen saturation 75%). Clinical examination reported blunt thoracic trauma with evidence of left pneumothorax. Patient stabilization was performed through crystalloid administration, pelvic binder placement, percutaneous left pneumothorax decompression before sedation and endotracheal intubation. The patient arrived at the emergency department 30 minutes after the trauma under stable condition. Immediately after the hospital arrival the patient underwent a whole-body CT-scan that showed subcutaneous emphysema, bilateral pulmonary contusions, a slight apical left pneumothorax and pneumomediastinum, fracture of the right sacral wing. First head CT scan resulted negative (**Panel 1**).

Panel 1



In Panel 1 Figure A and B we report the CT scan collected at the hospital arrival. As shown subcutaneous emphysema, bilateral pulmonary contusions, apical left pneumothorax and pneumomediastinum were present. In Panel 1 figure C we report the first bronchoscopy collected. As shown the rupture of the left superior bronchus was located distal to the lower bronchus division (yellow arrow). Pulsating left pulmonary artery was identifiable through the superior bronchial rupture (red arrow).

At end of the CT scan the patient was admitted in the ICU. A thoracic drainage was then placed to drain the left pneumothorax. Flexible bronchoscopy was subsequently performed to exclude or confirm airway injuries as cause of the massive pneumomediastinum. A complete rupture of the left superior bronchus was found immediately distal to the lower bronchus division. Pulsating left pulmonary artery was identifiable through the superior bronchial rupture without signs of active bleeding. The patient underwent urgent thoracic surgery within 4 hours. Right lung selective ventilation was performed

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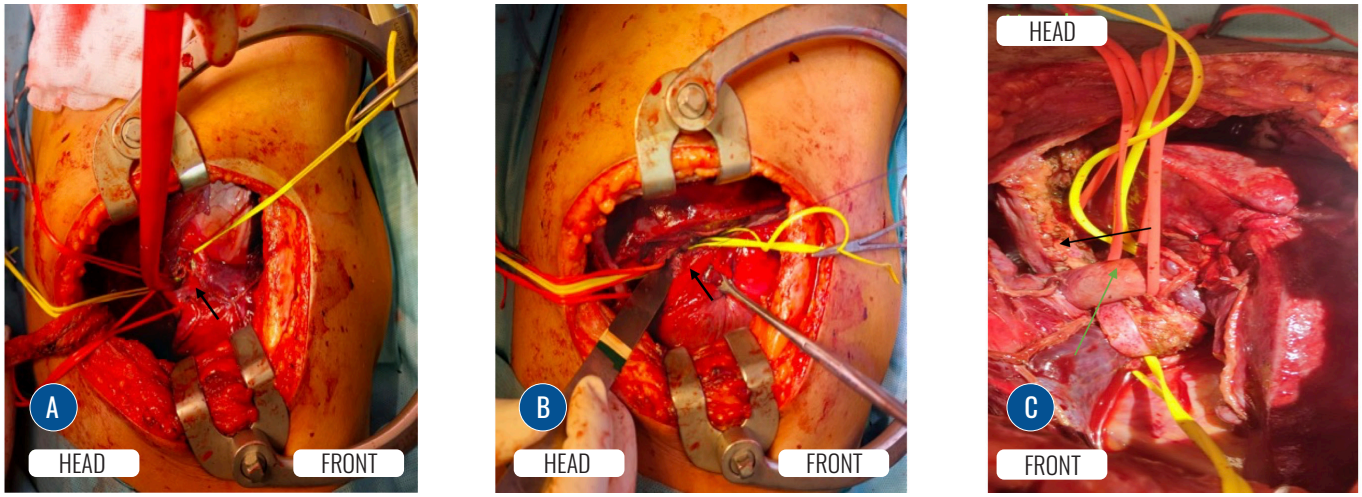
using a right double lumen endotracheal tube. After mediastinal and fissure dissection the left superior bronchus was visualized. A double running suture end-to-end anastomosis with 3-0 polydioxanone sutures (PDS) was performed. The sutures were covered with an intercostal muscle flap. The water test showed no air leakage. Two 28 French chest tubes were placed (**Panel 2**).

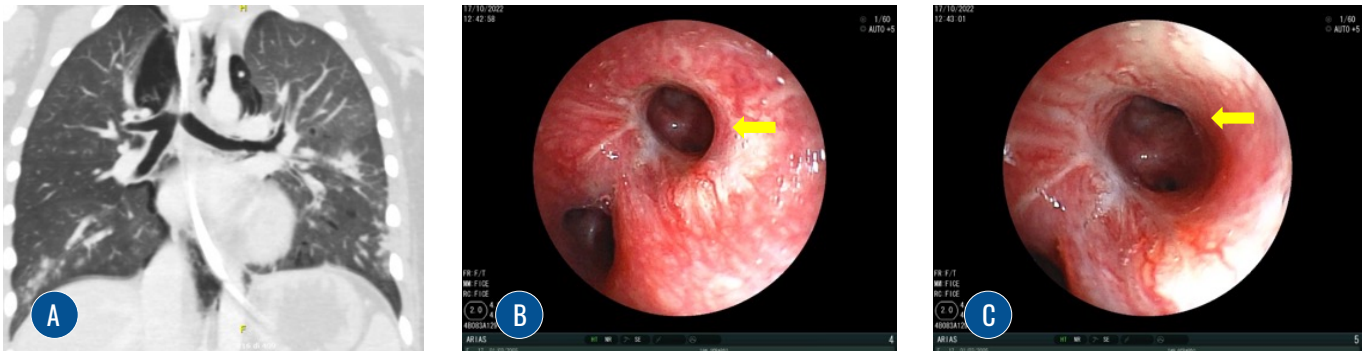
Panel 2



In panel 2 we report the three main intra-operatory phases. In Figure A the left superior bronchus (black arrow) is exposed after mediastinal and fissure dissection. In Figure B a double running suture is performed to obtain an end-to-end anastomosis of the left superior bronchus (Black arrow). In Figure C the Intercostal muscle flap (Black arrow) is placed to cover and protect the bronchial anastomosis, final view of the result with the pulmonary artery dissection in between the lobes (Green arrow).

At the end of the surgery, the double lumen endotracheal tube was then substituted with a normal single lumen endotracheal tube. Patient was ventilated under low PEEP (6 cmH2O) controlled protective ventilation for the first 48 hours of ICU stay. Chest X-rays controls performed in the first three days of ICU stay have shown left superior lobe contusion while flexible bronchoscopy controls revealed a normal transit through the left superior main bronchus. No signs of air leakage were present after surgery. Left superior lobe contusion spontaneously recovered within 4 days. Patient was then gradually weaned from mechanical ventilation (**Panel 3**).

Panel 3



In Panel 3 Figure A we report the CT scan collected after urgent thoracic surgery (left superior bronchial suture).
In Panel 3 figure B and C we report the bronchoscopy collected after thoracic surgery. As shown normal anatomy was restored, no signs of bronchial stenosis were found.

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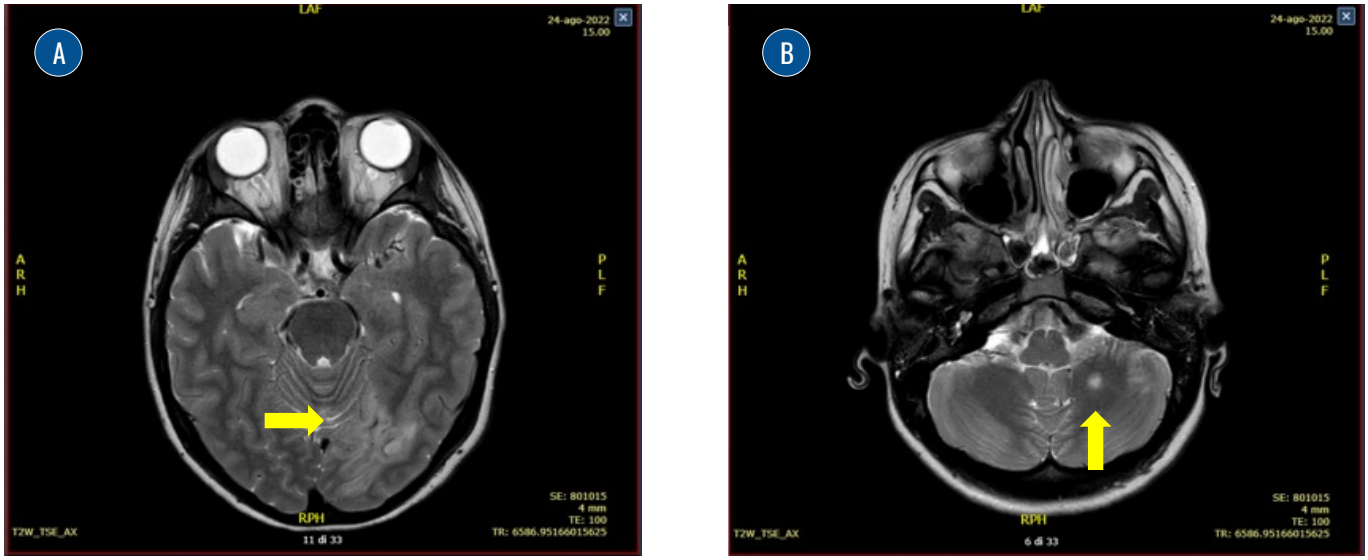
2.2 Cerebral air embolism after traumatic bronchial rupture

The first total body CT scan was performed at the patient's hospital arrival. No cerebral abnormalities were found. A second total body CT control was performed 10 hours and 24 hours later. Both controls documented a large area of cortico-subcortical ischemia in the left temporo-occipital lobe. The neurological examination was possible only 48 hours after surgery due to the respiratory problem which required deep sedation and controlled protective mechanical ventilation. Patient appeared conscious, oriented and without any focal abnormalities in the first examination and during the following ones. Cerebral MRI, performed on day 6, showed a hyperintensity in the left mesial temporo-occipital and left mesial parietal cortex, in addition to some focal hyperintense areas in the left cortical-subcortical cerebellar hemisphere and in the left medulla compatible with multiple ischemic lesions (**Panel 4**).

Panel 4



In panel 4 we report the cerebral MRI collected on day 6 after finding an ischemic area in the left parieto-occipital lobe during the control CT scan. As shown the lesion appears in the MRI as an hyperintensity lesion in the left mesial temporo-occipital lobe (yellow arrow figure A). A further focal hyperintense lesion was found in the left cerebellar hemisphere (yellow arrow figure B)

Hypothesizing a paradoxical embolism, we performed a compressive ultrasound sonography. No signs of deep venous thrombosis were found. Dimer dosage was elevated on the day of arrival (8130 ng/mL), and it progressively lowered to 2500 ng/mL. Transesophageal echocardiography (TEE) did not find any sign of interatrial or interventricular defect (color-doppler and positive pressure bubble test). No clinical sign or risk factors for fat embolism were present (long bone fracture, low platelet count, sub cutaneous or sub conjunctival petechiae) as well as fat embolism MRI signs. After the resolution of the respiratory failure, the patient was completely weaned from intravenous sedation and mechanical ventilation. Endotracheal tube was successfully removed on day 11. Patient was discharged to the thoracic surgery ward on day 16 after trauma. Patient was discharged to the child neuropsychiatry ward and finally to rehabilitation without any respiratory or neurologic sequelae. Follow up bronchoscopy was performed immediately before the hospital discharge two months after the trauma, no abnormalities were found.

3. Discussion

Tracheo-bronchial injuries (TBI) due to blunt chest trauma are a rare in the pediatric population. These injuries represent only 1-3% of pediatric blunt chest trauma, however, more than the 70% of the patients

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die before the hospital arrival [5-8]. Tracheo-bronchial injuries are usually associated with life threatening co-existing conditions which are responsible for the outcome like hemopneumothorax in 30% of cases, esophageal injuries (10%), major vascular injuries (20%), cardiac injuries (5%), spinal cord damages (5%) and abdominal injuries (20%). Early recognition and diagnosis are cornerstones in this type of trauma. The presence of pneumomediastinum and/or subcutaneous emphysema strongly suggests an airway injury. Flexible bronchoscopy is the gold standard for rapid recognition and fine characterization of these lesions [3,5]. Management of these patients range from conservative treatment if a condition of hemodynamic stability is resumed, to emergent surgical approach [3,7,8]. Thoracotomy is the option and end-to-end anastomosis represents the standard treatment. Running suture is indicated for the linear section of the bronchus. On the other hand, interrupted sutures seem to achieve better results when the bronchial tissues are traumatically damaged and/or the anastomosis needs more tension [9]. Airways anastomosis have always been considered at high risk for the several complications, dehiscence with consequent infection and erosion of the adjacent vessels representing the main ones. Covering and protecting the sutures may lead to better outcomes. The possible options include intercostal muscle flap, pericardial or pleural flap, omentum, pericardiophrenic pedicled graft (when pneumonectomy is performed) [10].

As far as the cerebral ischemia is concerned, this cannot be justified by a paradoxical thromboembolic event, given the absence of deep venous thrombosis and intracardiac shunt, while the absence of long bone fractures and the MRI findings do not support the hypothesis of a fat embolic event. We have hypothesized a cerebral air embolism as cause of the brain lesion given the context of chest trauma complicated by the rupture of a main bronchus. Systemic Air Embolism (SAE) represents a rare but potentially life-threatening complication of thoracic trauma with a mortality rate of 80% for blunt forms and 45% for penetrating forms in adult population [11]. Data about SAE in pediatric population after blunt chest trauma are missing. SAE after trauma can occur when gas penetrates in the venous system after veins disruption. Normally air embolies reaching the pulmonary filter pass to the peripheral tissues passing from the venous to the arterial circulation through cardiac shunt (inter-ventricular defects or inter-atrial defects). The consequent ischemia is caused by the vessel occlusion [12]. In the described case, thoracic trauma caused the complete avulsion of the left superior bronchus, and it could have involved minor pulmonary arteries and veins leading to a direct communication between the airway and the pulmonary veins (left circulation). During positive pressure ventilation the airway pressure easily overcomes the pulmonary vein pressure (left atrial or wedge pressure) generating the pressure gradient necessary to the direct gas entry in the arterial circulation [12,13]. This hypothesis could justify systemic embolism in the absence of intracardiac shunt. To corroborate the diagnosis no new cerebral ischemic lesions were found after the total restoration of the normal bronchial anatomy. It is finally necessary to underline that no stringent criteria or specific exams are available for the diagnosis of cerebral air embolism. Its diagnosis, necessarily obtained by exclusion criteria, still remains in the hypothetic field. In this case cerebral air embolism sings were detected incidentally and already after surgery. However, it is worth to underline that a rapid recognition of air embolism as consequence of traumatic tracheobronchial injury may represent a further indication for reparative approach. Its presence could suggest the need of an urgent etiological cause resolution.

4. Conclusion

Tracheo-bronchial injuries represent a serious possible complication in blunt chest trauma and its rapid recognition and treatment are crucial for patient survival. Fibro-bronchoscopy represents the gold standard for a clear characterization of the injury. In patient with unstable airway or severe respiratory conditions surgery should be performed as soon as possible. End-to-end anastomosis seems to achieve the best results. We strongly recommend to protect the anastomosis with a peduncled, well-perfused tissue.
SAE should always be suspected in case of chest trauma, especially if pneumomediastinum and/or subcutaneous emphysema are present. Tracheal and/or bronchial lesions should always be investigated.

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If possible, a neurological examination should be performed as soon as possible or, if discontinuing sedation is not possible, a cerebral CT scan should be considered. Rapid recognition of the bronchial rupture and consequent urgent surgery were crucial in this case. Rapid removal of the cerebral embolism cause avoided further brain damage.

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Abbreviations:

Computed Tomography (CT), Magnetic Resonance Imaging (MRI), polydioxanone sutures (PDS), Systemic Air Embolism (SAE), Glasgow Coma Scale (GCS), Intensive Care Unit (ICU), transesophageal echocardiography (TEE)

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CASE REPORT

Gemella sanguinis: endocarditis, hypercoagulability, and stroke. First case report in Italy.

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Abstract

Endocarditis is a severe life-threatening infection. In the last decades *Gemella sanguinis* became a rare new cause of infective endocarditis. We here describe the first case report of endocarditis by *Gemella sanguinis* in Italy with multiple complications including stroke and thromboembolism at multiple sites in the presence of a high resistance to heparin administration. Cardiac surgery, antibiotics and anticoagulation allowed to reverse the clinical complication and to improve the patient outcome. However, antibiotic prophylaxis in the presence of congenital or acquired cardiac risk factors of endocarditis and surgical oral or dental procedures should be strictly provided.

Introduction

Endocarditis is one of the most severe life-threatening infections after pneumonia, sepsis and intraabdominal abscesses. *Staphylococcus aureus* is the most involved pathogen, followed by *Streptococci viridans, Streptococcus bovis* and HACEK group. [1] In the last decades *Gemella sanguinis* became a rare new cause of infective endocarditis. Before rRNA and DNA sequencing in 1988 the *Gemella* species were misrecognised with the *Neisseria* genus or *Streptococcus* genus due to similarities in gram coloration and colonial morphology. [7,22]

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Gemella sanguinis (G. sanguinis) is a catalase-negative, facultative anaerobic, gram-positive coccus. It was first isolated and described in 1998 from six human blood cultures. Until that moment three strains of the same genus were known: *Gemella haemolysans*, *Gemella bergeriae* and *Gemella morbillorum* and other five species besides *Gemella sanguinis* have been recognized so far: *Gemella assacharolytica*, *Gemella taiwanensis*, *Gemella parahaemolysans*, *Gemella palaticanis*, *Gemella cuniculi*. Although being commensals of the oral cavity, gastrointestinal and genitourinary tract, these different strains of *Gemella* were described as the cause of different cases of endocarditis and opportunistic infections in immunocompromised patients, including arthritis, osteomyelitis, meningitis. [3] To our knowledge, from the first case described in 1998 until today fifteen cases of infective endocarditis related to *G. sanguinis* were reported in the literature around the world. [2-16] We describe the first case of endocarditis from *G. sanguinis* ever reported in Italy.

Case report

A 52-year old woman was admitted to the emergency department (ED) of Moriggia Pelascini Hospital in Gravedona (Como) with a right hemiplegic syndrome and aphasia and a history of recurrent episodes of fever treated with antibiotics in the previous days. Past medical history reported appendicectomy and thyroidectomy with subsequent thyroid hormone replacement therapy. Two months before the event the patient underwent multiple dental extractions. At the ED computed tomography revealed a left middle cerebral artery acute ischemic stroke, that was treated with mechanical thrombectomy after the patient tranfer to Sant'Anna Hospital, Como (**Figure 1**).

In the meantime, a transthoracic and transoesophageal echocardiography unveiled a large vegetation (2.4 x 2.4 cm) on the posterior leaflet of the bicuspid aortic valve leading to severe aortic insufficiency (**Figure 2 panel A-B**). Vancomycin, gentamycin, and ceftriaxone were empirically started. Gentamycin was then discontinued after the isolation of *Gemella sanguinis* in the blood culture.

FIGURE 1 - Left cortical-subcortical hypodensity related to a subacute ischemic lesion at the first hospital admission.

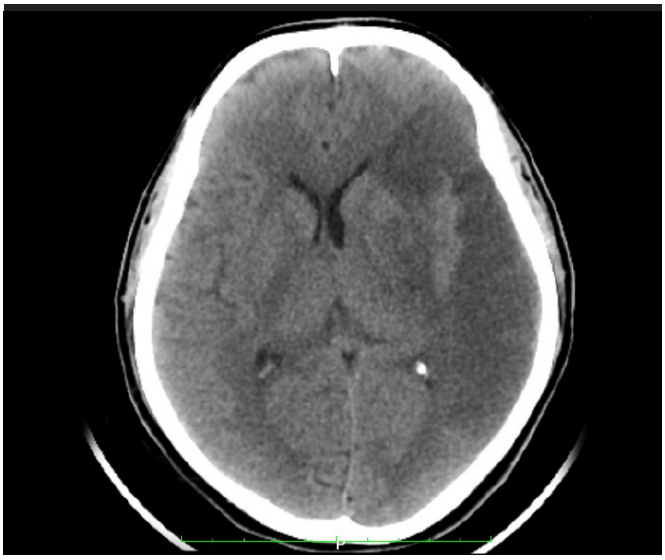
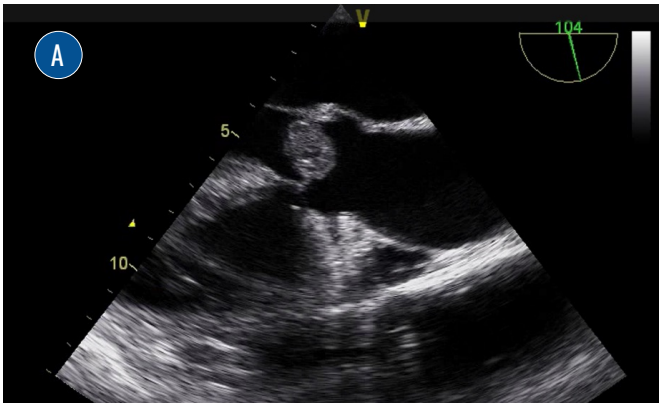
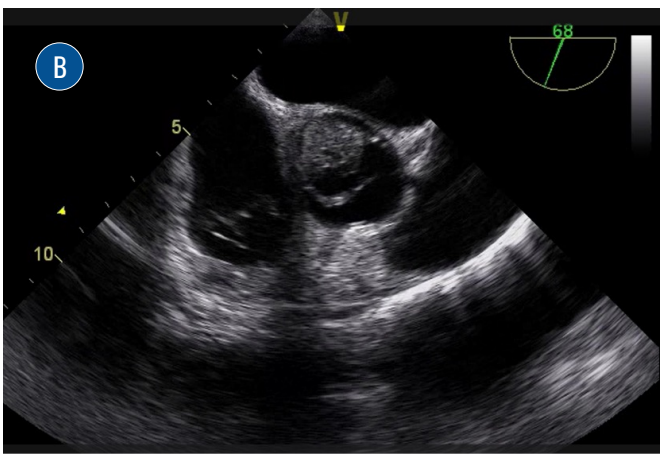


FIGURE 2 - Aortic valve vegetation during transesophageal echocardiogram. Left Panel (A), Mid-Esophageal Transgastric View; Right Panel (B), Mid-Esophageal Aortic Valve Short Axis View.





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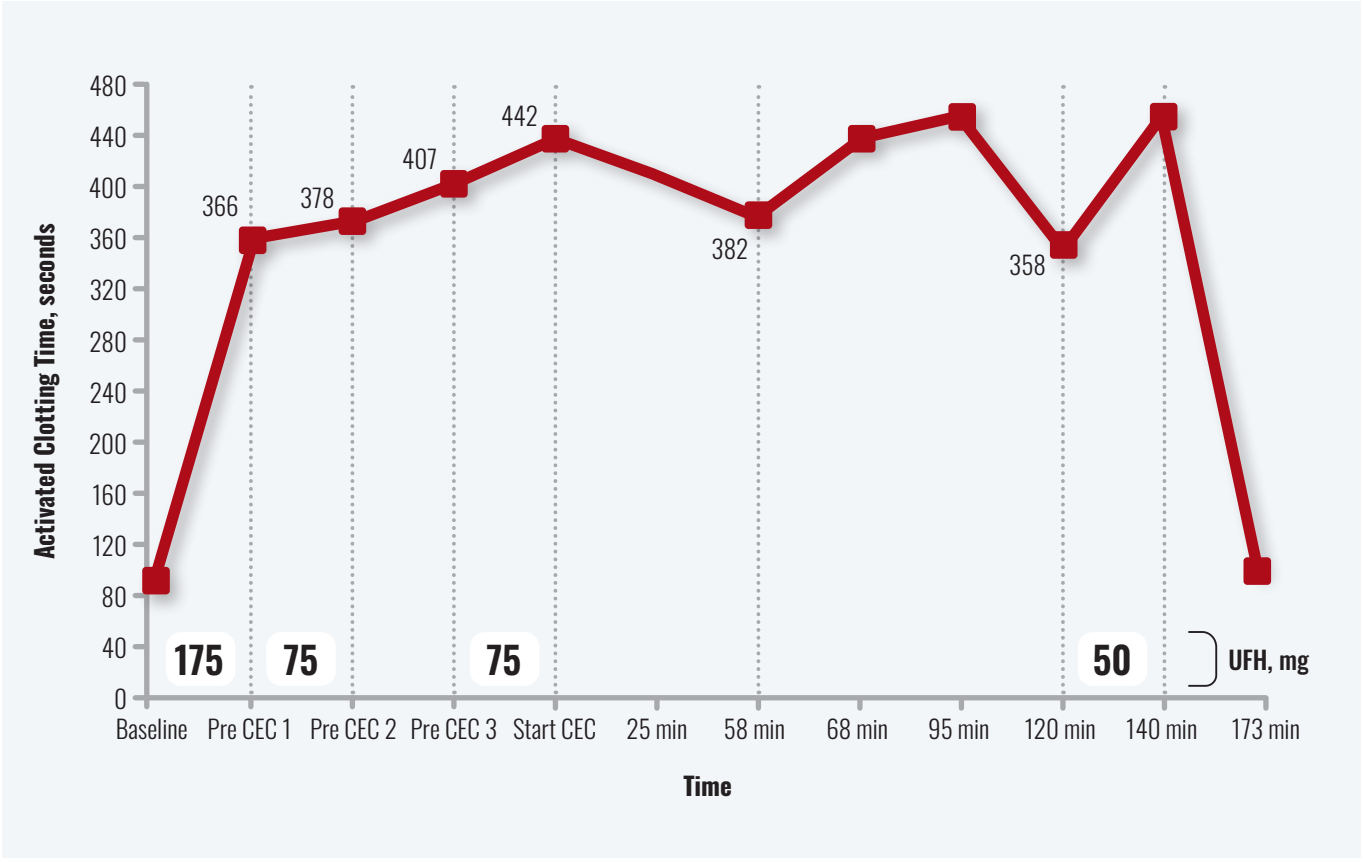
The patient was diagnosed with infective endocarditis according to the positivity of one major Duke's criterion (i.e. evidence of endocardial involvement) and three minor criteria (i.e. positive blood culture, an embolic phenomenon, and a congenital heart condition).
During the hospitalization the patient developed deep venous thrombosis in the left femoral vein, pulmonary thromboembolism, interstitial pneumonia, urinary tract infection and atrial fibrillation. Therefore, therapeutic anticoagulation with low-molecular-weight-heparin and antiarrhythmic therapy with amiodarone were started.

She was finally admitted to Niguarda hospital where she underwent aortic valve replacement with a mechanical valve and after the drainage of a perianular abscess. During surgery a significant heparin resistance required the administration of multiple additional boluses of unfractionated heparin besides the initial one until a total dosage > 800 UI/Kg and 500 UI of ATIII to achieve and maintain an ACT ≥ 400 seconds before and during extracorporeal circulation (**Figure 3**). The major cardiac surgery intervention was successful and ten days after the patient was discharged to a cardiac rehabilitation centre.

FIGURE 3 - Trend of measured activated clotting time (ACT) before and after administration of unfractionated heparin (UFH) boluses during extracorporeal circulation.



Discussion

Fifteen cases of infective endocarditis from *Gemella sanguinis* were reported in the literature until today. Most of them involved mainly the aortic valve and to a lesser extent the mitral valve. Only one case affected the tricuspid valve. All the reported endocarditis processes regarded natural valves, except in the case of involvement of two prosthetic valves. Half of patients had previous congenital or acquired cardiac risk

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factors, such as rheumatic heart disease, bicuspid aortic valve, and degenerative valvular disease. One out of two patients had a poor oral hygiene with dental caries, periodontal disease or underwent dental procedures shortly before developing the infection.

The treatment was usually surgical with valve replacement in addition to long term combined antimicrobial therapy with ceftriaxone, penicillin G, vancomycin, daptomycin or gentamycin. [2-16]

Our case report describes the first available evidence of complicated endocarditis by *Gemella sanguinis* in Italy.

According to the AHA recommendation, antibiotic prophylaxis for dental procedures should be strictly considered in patients with a high risk of adverse outcome from endocarditis, such as those with prosthetic cardiac valve, previous or recurrent infective endocarditis, cyanotic congenital heart disease or valvulopathy after cardiac transplantation. [17,18]

Active infective endocarditis was demonstrated to be an independent risk factor for heparin resistance, due to an hyperinflammatory state that causes acute-phase proteins increase with neutralization of heparin's activity and hypercoagulation due to the activation of platelets and reduced ATIII activity. Lower albumin level, preoperative heparin use, and high platelet count have also been associated with reduced heparin responsiveness. [19,20] It has been reported a potentiation of the heparin activity after the administration of 1000 UI of ATIII concentrate in patients with initial failure to obtain therapeutic anticoagulation with the usual dose of heparin before cardiac surgery. [21] Identification and treatment of potential correctable risk factors for heparin resistance could be useful before starting cardiac surgery even in patients with uncomplicated infective endocarditis.

Conclusions

In conclusion, although infective endocarditis by *Gemella sanguinis* has usually a good outcome after combination of surgery and prolonged antimicrobial therapy, clinical consequences of bacteremia by *Gemella sanguinis* can be devastating. Therefore, oral and dental care and treatment should be considered in the presence of congenital or acquired cardiac risk factors and antibiotic prophylaxis during dental extraction should be strictly provided.

Authors' contribution

L.A. interpreted data and wrote the manuscript; T.C. collected and interpreted data and reviewed and edited the manuscript; F.C. collected radiological data and reviewed and edited the manuscript; M.P.G. interpreted data and reviewed and edited the manuscript; F.M. collected and interpreted data, reviewed and edited the manuscript and conceived the case report; E.R. collected, analyzed and interpreted data, wrote the manuscript, conceived and supervised the case report.

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BRIEF ARTICLE

Emerging cause of acute metabolic acidosis in the ICU

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Abstract

Background: Metabolic acidosis is a frequently encountered finding in patients admitted to Intensive Care Unit (ICU). The etiological differential diagnosis of metabolic acidosis includes a relatively frequent and often unknown clinical condition which is represented by starvation ketoacidosis. Starvation ketoacidosis (SKA) occurs after the body is deprived of glucose as the primary source of energy for a prolonged time, and fatty acids replace glucose as the major metabolic fuel. We conducted a retrospective observational study we screened medical records of patients admitted to ICU from 2022/10/10 to 2023/04/10, including patients with metabolic acidosis, with ketonuria detected by urine samples or urine stick positivity treated with glucose solutions or enteral/oral nutrition within 2 hours of diagnosis. The primary outcome was to evaluate the prevalence of ketoacidosis in critically ill patients; the secondary outcome was to evaluate the impact of ketoacidosis on hemodynamic instability and the role of early treatment in reducing complications and days of hospitalization in ICU.

Results: In the time period studied, 574 patients were admitted to the ICU, 90 patients had diagnostic criteria for ketoacidosis (15,67%) of which, 19 patients met inclusion criteria. Of these patients 11 were hemodynamically stable and 8 unstable. The unstable patients had a mean norepinephrine support of 0,21 mcg/kg/min. Unstable patients had lower BE value than stable patients (-5,4 vs -1,7, p =0,3), lower pH (7,28 vs 7,33, p=0,13), significantly lower serum albumin (24,5 vs 30,7, p =0,03) and lower HCO3- (20,5 mmol/L vs 24,5, p = 0,21). No statistically significant differences were found in the absolute value of ketonuria (unstable 42,3 vs stable 45,7, p= 0,90) or in the lactate levels at admission.

Conclusion: The presence of ketonuria shows that our patients are often fasting for a variable time lapse depending on the reason for hospitalization, the days of hospitalization preceding entry into the ICU, and the underlying clinical conditions. In our analysis we found that acidosis can lead to transient hemodynamic instability, early treatment could avoid several complications as acidotic electrolyte disorders or major cardiac events related to amine use and could short ICU length of stay or unnecessary ICU admission.

Keywords: metabolic acidosis, starvation ketoacidosis, ketone bodies.

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Background

Metabolic acidosis, defined as the presence of an acid-base imbalance associated with serum reduction of bicarbonate concentration and low pH is a frequent finding in patients admitted to the intensive care unit (ICU) [1]. The most frequent causes of acute metabolic acidosis are sepsis, acute renal failure, drug intoxication, hypovolemia, hemorrhagic shock, cardiac arrest, diabetic ketoacidosis.

This acute metabolic acidosis is a potentially life-threatening condition with several clinical manifestations as myocardial disfunction, cerebral edema, pulmonary vasoconstriction, systemic vasodilatation and fatal arrhythmias [2,3].

A differentiation has recently been introduced in the diagnostic criteria of metabolic acidosis, distinguishing a moderate and severe form based on clinical severity: moderate metabolic acidosis (pH<7.30, base excess < −4 mmol/l and $PaCO^2 \leq 45$ mmHg) occurs in 8,4% of patients admitted to the ICU while severe metabolic acidosis (pH < 7.20, $PaCO^2 < 45$ mmHg, HCO3- < 20 mmol/L and total Sequential Organ Failure Assessment [SOFA] > 4 OR Lactate > 2mmol/L) occurs in 1.5 % of patients. The ICU and hospital mortality rates were 19% and 45%, respectively [4].

In ICU patients, moderate or severe metabolic acidosis seems to be associated with high mortality and increased length of stay [5,6].

Diabetic Ketoacidosis is a life-threatening condition that mostly affect patients with uncontrolled diabetes and it is characterized by hyperglycemia, acidosis and high levels of serum and urinary ketone bodies [7]. However, in several ICU patients, a relatively frequent and often misdiagnosed condition of metabolic acidosis with high serum/urinary ketone levels and normal/low blood glucose level is due to starvation ketoacidosis. Starvation ketoacidosis (SKA) occurs after body is deprived of glucose as the primary source of energy for a prolonged time, and fatty acids replace glucose as the major metabolic fuel. SKA can be also associated to new eating habits such as high-protein diets, low-carb diets, ketogenic diets, intermittent fasting, to the use of drugs that can induce starvation, to the lack of adherence to the Eras protocols [8] and to the late presentation of patients to the hospital after the onset of symptoms. Studies on starvation ketoacidosis are lacking and limited to few case reports [9]. Early recognition and treatment of this condition could prevent several life threating complications, improve survival and shorter the ICU length of stay.

The primary outcome was to evaluate the prevalence of ketoacidosis in critically ill patients admitted to intensive care unit. The secondary outcome was to evaluate the impact of ketoacidosis on hemodynamic instability (MAP < 65 mmHg unresponsive to filling with crystalloids, requiring start of aminic support with noradrenaline and/or other vasopressors as required by normal clinical practice) and the role of early treatment in reducing these complications and the days of hospitalization in intensive care unit.

Materials and methods

We conducted a retrospective observational study. The research protocol was approved by the Local Ethics Committee of Bologna (approval number CE AVEC 519-2023-OSS-AUSLBO of 2023/07/27). We screened all admissions and medical records of patients admitted in the ICU (Ospedale Maggiore-Bologna, Italy) from 2022/10/10 to 2023/04/10. We included patients of more than 18 years old who were admitted to intensive care unit with metabolic acidosis, with ascertained ketonuria detected by urine samples or urine stick positivity and who were treated with glucose solutions or enteral/oral nutrition within 2 hours of diagnosis. We excluded patients with severe renal injury (KDIGO III/IV/V), BPCO Gold classification 3/4, acute drugs intoxications and uncontrolled diabetes. Patients were differentiated into two groups: surgical patients, if admitted to ICU after surgery for monitoring of vital signs or need for intensive treatment, and medical patients. We also assessed each patient if hemodynamic unstable (defined as hypotensive state, with mean arterial pressure < 65 mmhg, unresponsive to volume expansion and requiring norepinephrine support). We collected data at admission and after 12 h: pH, BE, HCO3-, Hb, ketonuria, lactates, albuminemia, $PaCO^2$; we collected the different kind of treatments and their duration to restore a normal pH and to reduce ketonuria.

Data are presented as percentage and numbers,

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means and standard deviations, medians and interquartile ranges. Groups comparisons were performed using chi square test or Fisher exact test for categorical variables and student t-test for normally distributed data. P-value < 0,05 was considered statistically significant.

Results

In the study period 574 patients were admitted to the ICU, 90 patients with diagnosis of ketoacidosis (15.67%) of which, 16 patients met inclusion criteria.
The overall patients' characteristics are shown in **table 1**.

TABLE 1 - patients baseline characteristics at ICU admission

	Tot(n=19)	Stable (n=11)	Unstable (n=8)	P value
Age	57	51	63	0.09
Male	7	4	3	
Surgical patients	10			
Medical patients	9			
Norepineprhine (mcg/kg/min)		0	0.22 ± 0.19	
pH		7.33 ± 0.07	7.28 ± 0.06	0.13
HCO3- (mmol/l)		24.5 ± 6.6	20.5 ± 6.4	0.21
BE (mmol/l)		-1.7 ± 6.6	-5.4 ± 8.3	0.34
Albumin (g/l)		30.7 ± 6.2	24.5 ± 5.4	**0.03***
Lactate (mmol/l)		1.5 ± 2.3	3.1 ± 3	0.23
Creatinine (mg/dl)		0.7 ± 0.4	1.1 ± 0.4	0.06
Hemoglobin (gr/dl)		12.2 ± 2.6	10.4 ± 1.8	0.1

*P value < 0,05

They were 7 men and 12 women, mean age was 56. Three patients had cancer, and 8 underwent major surgery.
Of these patients 11 were hemodynamically stable and 8 unstable. The unstable patients had a mean norepinephrine support of 0.22 mcg/kg/min. Unstable patients had lower BE value than stable patients (-5.4 vs -1.7, p =0.3), lower pH (7.28 vs 7.33, p=0.13), significantly lower serum albumin (23.3 vs 30.4, p =0.04) and lower HCO3- (20.5 mmol/L vs 24.5, p = 0.2). No statistically significant differences were found in the absolute value of ketonuria (unstable 42.5 vs stable 44.5, p=0.90) or in the lactate levels at admission.
Comparing medical (8) and surgical patients (11): the medical patients had a lower ketonuria (12 versus 71 p 0.009) and an higher HCO3- (26 versus 20 p 0.04). (**Figure 1**)
All the patients were treated with 12 h infusion of glucose solutions 5% or 10% at different rates (100-125ml/h, with a total administered volume of 1000 ml) or with enteral feeding (both trough nasogastric/nasojejunal tube) or oral feeding.
After 12 h of treatment all patients improved, amine support was suspended in unstable patients and normal pH was restored. No differences were found in ICU staying between the groups. (**Table 2**)

Discussion

Nineteen patients were admitted to ICU with ketonuria at admission and were treated early with caloric support. The presence of ketonuria in our patients shows that our patients are often fasting for a variable time lapse depending on the reason for hospitalization, the days of hospitalization preceding entry into the ICU, and the underlying clinical conditions.

FIGURE 1 - Ketonuria and HCO3 in surgical and medical patients

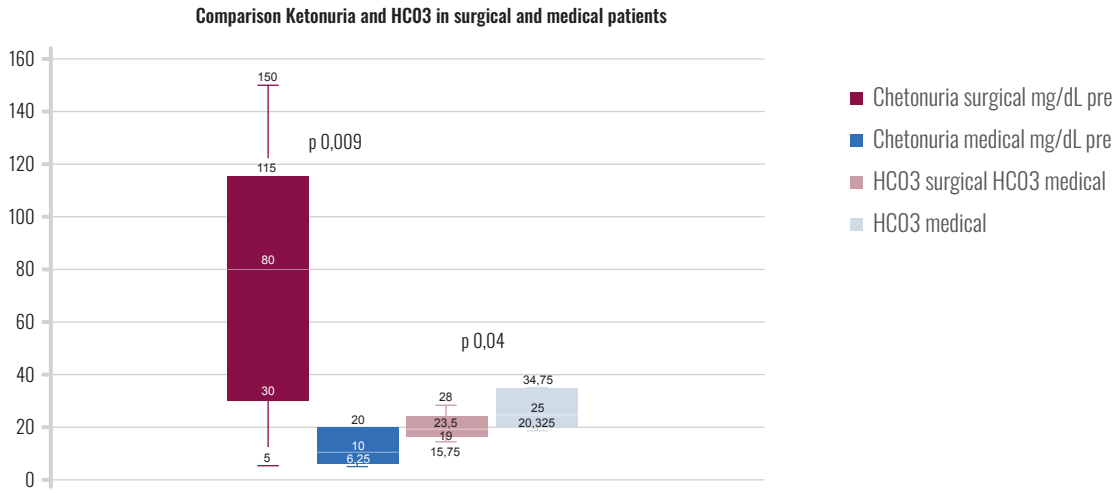

TABLE 2 - patients characteristics after 12 h of treatment

	Tot(n=19)	Stable (n=11)	Unstable (n=8)	P value
pH post		7.40 ± 0.03	7.42 ± 0.03	0.1
BE post (mmol/l)		-0.28 ± 4.2	-2.3 ± 2.3	0.54
HCO3- (mmol/l)		24.7 ± 3.8	22.3 ± 2.6	0.25
Lactate (mmol/l)		1.17 ± 0.6	3.02 ± 4	0.28
ICU LOS mean		2.4	6.1	0.1
Treatment				
-Enteral nutrition		0	1	
-Oral nutrition		4	0	
-Parenteral glucose 5%-10% infusion		7	7	

These conditions are usually added to a hypercatabolic state in which there is a metabolic and hormonal dysregulation in response to stress (e.g. surgery, sepsis, trauma) [10-11].

In healthy adults, in case of prolonged fasting, glucose deficit activates gluconeogenesis and inhibits glycolysis; the Krebs cycle is inhibited (due to lack of oxaloacetate which is oxidized to phosphoenolpyruvate for gluconeogenesis) and the excess AcetylCoA is used for the synthesis of ketone bodies: acetoacetate, betahydroxybutyrate, and acetone (metabolically inert, excreted with exhalation). The activation of lipolysis detemines the transport of free fatty acid chains to the liver mitochondria where they undergo beta-oxidation [12-13].

Under normal conditions, the production of ketone bodies is a protective mechanism; in fact, in the absence of glucose, ketone bodies can be used as an energy substrate and limit the catabolism of amino acids for energy production [14]. Furthermore, in healthy adults, increased blood ketone concentration inhibits further activation of lipolysis, increases insulin production and inhibits further formation of ketone bodies [15,16]. It has been demonstrated that ketone bodies also have an antioxidant effect, indeed, they activate autophagy processes that are involved in the maintenance of

cellular integrity, in the eradication of toxins, cancerous molecules and intracellular damage. Ketogenic diets developed from these mechanisms [17-20]. In cancer patients, ketone bodies could have a protective role, especially for the activation of autophagy [21,22]; in patients with neurovegetative disease a state of ketosis can lead to a reduction of the inflammatory mechanisms involved in the pathogenesis of the disease [23].

In some clinical conditions, ketogenesis is activated early, as in pregnant women and in children [24,25]. Excessive production of ketone bodies can lead to ketoacidosis, a condition of metabolic acidosis with reduced concentration of bicarbonates and excess bases. There are at least two other causes of metabolic ketoacidosis: alcoholic ketoacidosis (AKA) and diabetic ketoacidosis (DKA) [26]. The first occurs in patients with a history of chronic alcohol abuse and usually ketoacidosis is associated with increased lactate levels; indeed, ethanol is metabolized to both acetaldehyde and lactic acid [27]. The second occurs in patients with type 1 or type 2 diabetes mellitus on insulin therapy in which the deficit of insulin production results in an inability of the tissues to use circulating glucose and in an increased production of ketone bodies which can lead to ketoacidosis, usually characterized by hyperglycemia, decreased blood bicarbonate level, high ketone levels and insulin deficiency. A state of "euglycemic" diabetic ketoacidosis can also occur in patients with type II diabetes treated with oral hypoglycemic drugs inhibitors of the sodium- glucose transporter type 2 (SGLT-2), in this case, blood glucose levels are usually normal [28]. Sometimes these causes of acidosis coexist, and it is not possible to make a differential diagnosis; it is also always necessary to exclude all other causes of metabolic acidosis (ethylene glycol, methanol, acetylsalicylic acid, tricyclic antidepressants, etc.) [29-33].

Fasting ketoacidosis (Starvation Ketoacidosis, SKA), often misdiagnosed, can cause acidosis that is unresponsive to volume expansion and bicarbonate administration and can determine hemodynamic instability and consequent hospitalization in an intensive care environment. Patients in the perioperative period, those suffering from pancreatitis [34,35] and septic patients seem to be more exposed to this risk, probably due to stress-induced dysregulation (increased levels of cortisol, decreased insulin/glucagon ratio). The resolution of this acidosis is rapid after administration of glucose or re-feeding, indeed, the increase in blood glucose concentration corresponds to an increased production of insulin and a reduction in the production of glucagon; in the absence of specific guidelines for the treatment, glucose infusion is used as suggested by the guidelines for diabetic ketoacidosis. Ketoacidosis is little studied perioperatively as an index of malnutrition.

In our analysis we found that acidosis can lead to transient hemodynamic instability and most of the unstable patients have low levels of albuminemia and are, thus, malnourished.

Early treatment could avoid several complications as acidotic electrolyte disorders or major cardiac events related to amine use and could short ICU length of stay or unnecessary ICU admission. In fact, in our results hemodynamic stable and unstable patients, both early treated, had the same ICU loss. Our study has several limitations, it is a retrospective observational study, there is a small sample of patients, and the treatments were different depending on clinical practice and different clinicians.

Conclusion

In all patients with metabolic acidosis without an easily identifiable cause ketone bodies in urine or blood samples should be investigated. Indeed, although our series is numerically limited, it is interesting to consider how a simple treatment can resolve apparently complex clinical cases.

More studies are needed to have a comprehensive vision of the incidence of starvation ketoacidosis in ICU, to understand all the physiopatological effects of fasting and starvation in different subgroups of patients (i.e., surgical/medical/trauma patients) and to proper treat this condition.

Declarations

Ethics approval and consent to participate: The clinical study was approved by the Bologna ethics committee.

Consent for publication: not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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BRIEF ARTICLE

The role of sex in sample size determination

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Abstract

The sample size calculation in randomized clinical trials mainly depends on the incidence of the outcome measure in the control group. Sample size calculation should also take into account the differences in outcome rates between male vs. female genders. This issue is, however, often not considered, leading to over- or under-estimation of the outcome distribution and ultimately to underpowered trials with erroneous conclusions. Hence, this short article discusses examples related gender and sample size and provides indications for an optimal estimation.

Keywords: simple size, sex, gender

The size of your sample of patients for a randomized clinical trial on the effect of a treatment on an outcome measure depends on the incidence of the outcome measure in the control group. Therefore, you must determine the precise distribution of your outcome measure in the control population. Once you know this (e.g. 50% of the patients die), you can make an educated guess of the effect of the new treatment on this distribution - for instance mortality will be reduced to 40%). Currently, sample size calculations do not take into account the differences in outcome rates between the sexes, and calculate on the basis of the overall average of the population. This over- or under-estimation of the outcome distribution may lead to an underpowered trial, giving erroneous conclusions. Thus, it is inherently wrong to calculate sample sizes by just assuming males and females are similar.

An example: Atrial fibrillation (AF) is a common cardiac arrhythmia and is associated with a five-fold increase in risk of stroke. The increased risk depends on various stroke risk factors. Despite a higher reported prevalence of AF in males [1], several studies have described a higher risk for stroke in women than in men, especially in those aged 75 years or older. [2] The overall prevalence of

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AF with hospitalization in Lombardy was 2.4% between 2002 and 2013, the prevalence rising with age (0.39% <65 years and 8.45% ≥75 years). AF with hospitalization was more common in males (2.67%) than females (2.15%), p<0.001. Females were consistently older and had fewer risk factors for AF, such as hypertension and diabetes mellitus. A meta-analysis including 993,600 patients found a significantly higher risk of stroke in female AF patients (HR: 1.24, 95%CI: 1.14-1.36, p<0.001). [3]

This finding was confirmed by *Marzona et al.*; the cumulative risk for stroke was higher for females with AF, and on correcting for age, chronic HF, hypertension, diabetes mellitus, prior stroke, myocardial infarction, peripheral artery disease, chronic kidney disease, oral anticoagulant drugs and antiplatelet drugs, this increase in risk remained significant (HR: 1.18, 95CI: 1.14-1.21). [4]

If a RCT were to assess the effects of a certain treatment on the incidence of stroke in patients with AF, it would have to take account of the differences in the proportion of male or female patients who experience a stroke over the course of the trial. If we ignore the differences between sexes we could take the proportion of patients who experience a stroke as a whole: 20100/315383 - an incidence of 6.4%. [4] Using these data to estimate a sample size for a hypothetical trial in which we believe that our new treatment leads to a 25% relative risk reduction (RRR) of stroke, including standard parameter values (80% power and alpha 0.05), we would need to include 6282 patients (Table 1).

TABLE 1 - Sample size for stroke in patients with atrial fibrillation.

	TT control group	RRR	TT experimental group	Effect size	Power	α	N group	N total
All	6.4%	25%	4.780%	0.071	80%	0.05	3141	6282
Males	5.3%	25%	3.975%	0.063	80%	0.05	3935	7870
Females	7.4%	25%	5.550%	0.075	80%	0.05	2764	5528

Sample size calculation for categorical endpoint, proportion of stroke in AF patients was taken from *(Marzona et al., 2020)*. Analyses done using the pwr-package, pwr.2p.test-command in RStudio.

If someone ran the trial with 6282 patients, assuming equal distribution of the sexes, we would end up with 3141 males and 3141 females, of whom half are randomized to one treatment arm and half to the other. Any subgroup analyses for the effect of the treatment by sex on these small data sets would therefore be underpowered (Table 2).

TABLE 2 - Power calculation for stroke in patients with atrial fibrillation.

	N RCT	N group	π control group	RRR	TT experimental group	Effect size	α	Power
Males	3141	1570	5.3%	25%	3.975%	0.063	0.05	42.5%
Females	3141	1570	7.4%	25%	5.550%	0.075	0.05	56.0%

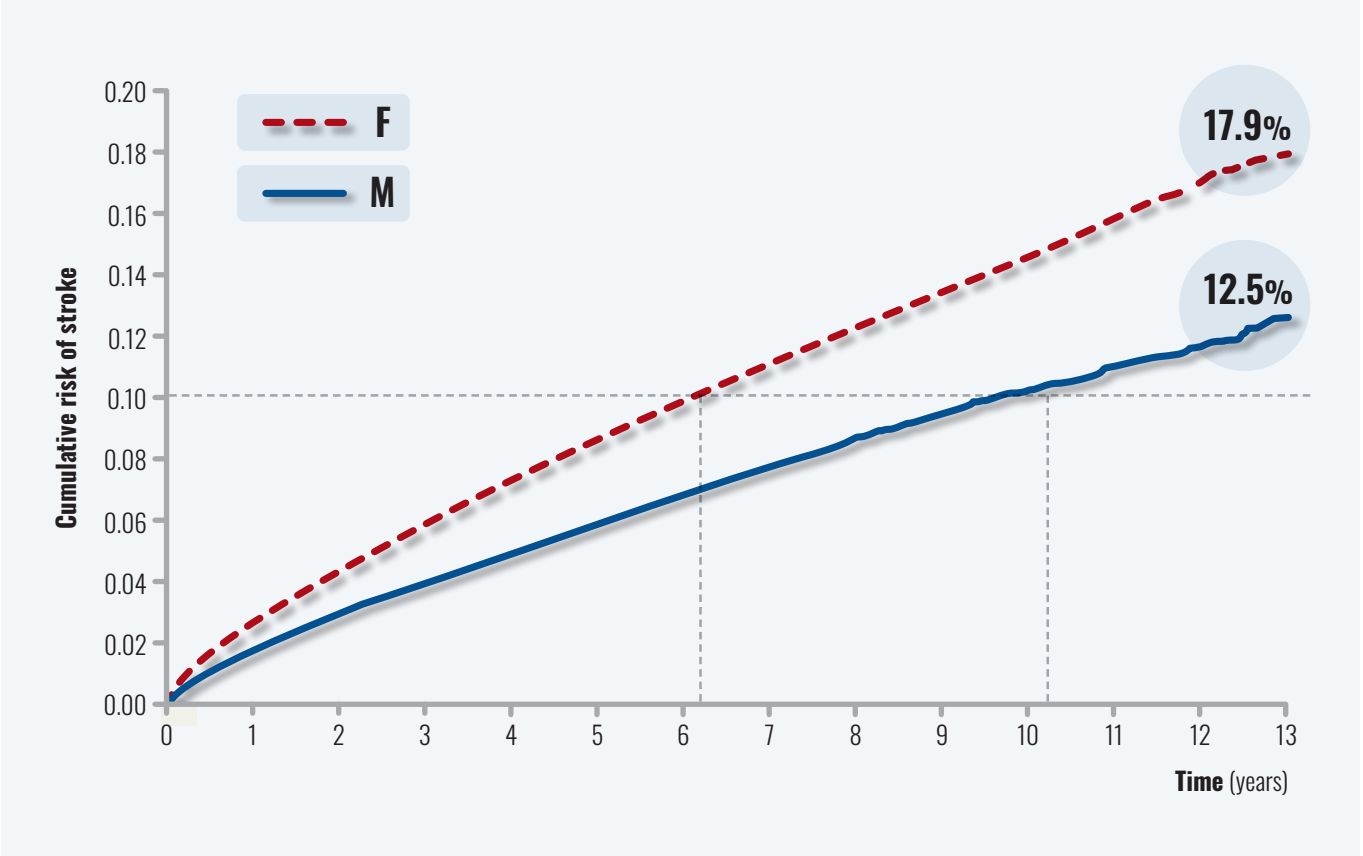
Analyses done using the pwr-package, pwr.2p.test-command in RStudio.

Here we calculated the power, assuming that the RRR would be 25% of our treatment. For males, the power is only 42.5%, meaning that the chances of a Type 2 error, accepting a false null hypothesis, is 57.5% (1-power). However, as we saw in the studies by *Marzona et al., 2018 and Marzona et al., 2020*, the proportions of AF patients who experience a stroke in the first 3.5 years of follow-up is not the same for both sexes: for males it is 5.3%, while for females it is 7.4%. [3,4] Applying the same assumptions, we would now "only" need to include 5528 female patients in our trial; however, based on the male event rate, 7870 males should be included (Table 1). Thus, if the

sample size (N=6282) calculated on the prevalence in the general population had been used, enough patients would have been included based on the female incidence of the endpoint, but with the male incidence of the endpoint the study would be underpowered.

The risk of all-cause death is high in males (though not significantly), and this may lead to a competing risk of death which prevents male AF patients developing a stroke. [3] When assessing the effect of a new treatment in these patients, a competing-risk assessment is needed. In addition, the higher risk of all-cause death in males with AF means that fewer males will complete the follow-up, so less data will be collected for male patients. Another point is the timing for the outcome event to present itself. Figure 1 shows the risk for stroke in AF patients over time by sex. [4] Females reach a cumulative risk of 10% in little over six years while males take more than ten years. These differences in time-to-event have to be taken in consideration when designing trials which include both males and females.

FIGURE 1 - Kaplan-Meier curves for stroke in AF patients, adapted from Marzona et al., 2020.



In conclusion, when assessing the effect of a treatment in a population including both sexes, a researcher should be aware of what proportion of the population may have competing risks. In addition, the timing of outcome events during follow-up should be borne in mind.

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REVIEW ARTICLE

2022 highlights in interventional cardiology

Novel concepts for multivessel coronary artery disease treatment, vascular access for coronary interventions, and heart valve interventions

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In 2022 much new evidence-based information related to coronary and structural interventions has been published, and several trials offered new therapies and practice-changing insights for patients with advanced ischemic and structural heart disease. Therefore, this review highlights some of the most exciting data from the latest published manuscripts in the interventional cardiology field. In our report, we tried to address the strengths and weaknesses of every piece of evidence, searching for a balance between nonconstructive criticism and easy enthusiasm.

Coronary artery disease treatment in patients with left ventricular dysfunction

Coronary artery disease is the most common cause of heart failure and is associated with poor survival and low quality of life despite advances in medical therapy[1]. In the ESC guidelines, coronary artery bypass graft (CABG) is recommended as the first revascularization strategy in patients with ischemic cardiomyopathy and multivessel disease as long as the risk of surgery is acceptable (class I, level of evidence B)[2,3]. Percutaneous Coronary Intervention (PCI) can be considered in one- or two-vessel disease when complete revascularisation can be achieved (or in three-vessel disease based on advice from the heart team). However, that recommendation is relatively weak (class IIa, level of evidence C). CABG is also recommended in the USA for the same clinical context, and no clear indication

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for PCI has been established due to limited evidence[4]. In 2022 the REVIVED-BCIS2 randomized controlled trial tried to shed light on this controversial topic. The study, whose protocol and results were published in the Journal of the American College of Cardiology[5] and the New England Medical Journal[6], claimed that PCI did not reduce all-cause mortality or hospitalizations for heart failure in patients with severe left ventricular dysfunction and extensive coronary artery disease. Restoring the patency of coronary arteries to improve blood supply to jeopardized, stunned or hibernating myocardium has long been considered a must-to-have treatment in this highest-risk patient population. In the STICH trial, coronary revascularization was accomplished through CABG, but treatment improved survival only in highly selected, typically young, patients. Moreover, the benefit needed a ten-year follow-up to emerge, probably due to the required time for CABG benefits to counterbalance the early surgical complications. PCI is from ever perceived as an attractive alternative to bypass surgery, as it might offer the benefits of revascularisation without the early surgical hazards[7, 8]. However, when dealing with patients with left ventricular dysfunction and obstructive coronary disease, no randomized evidence supports percutaneous revascularization, and according to expert opinion and local practice and expertise, this treatment is recommended only in selected patients.

The REVIVED-BCIS2 is the first adequately powered randomized trial to examine the efficacy and safety of PCI in patients with left ventricular systolic dysfunction and angiographically significant coronary artery disease[6]. The study enrolled patients with severe left ventricular dysfunction (ejection fraction 35% or below), extensive coronary artery disease, and demonstrable viability in at least four dysfunctional myocardial segments potentially addressable by percutaneous revascularization. Any commonly accepted diagnostic modality could assess viability, but cardiac magnetic resonance imaging was used the most. Recent myocardial infarction within four weeks, decompensated heart failure, or sustained ventricular arrhythmias within 72 hours were criteria for exclusion from the study. A total of 700 patients from 40 centres in the UK were randomly assigned in a 1:1 ratio to either PCI with optimal medical therapy or optimal medical therapy alone. The median age of participants was 70 years, 88% were men, and their mean left ventricular ejection fraction was 28%. The primary outcome was the composite endpoint of all-cause death or hospitalization for heart failure. Secondary outcomes included left ventricular ejection fraction at six and 12 months and quality of life measures. During a median follow-up of 3.4 years, the primary outcome occurred in 129 (37.2%) patients in the PCI group and 134 (38.0%) patients in the medical therapy alone group with a hazard ratio of 0.99 (95% confidence interval 0.78–1.27, p=0.96). No significant difference between groups was observed for the trial's most clinically significant secondary outcome, the left ventricular ejection fraction at six and 12 months.

Given that only patients with demonstrable myocardial viability were enrolled, the latter finding challenges the concept of myocardial hibernation. This phenomenon, first described by Rahimtoola in 1989[9], for decades has been considered an adaptation of the heart to cope with the effects of severe coronary disease, potentially reversible by restoring coronary patency[10]. Quality of life (the other most significant secondary outcome) favoured PCI at 6 and 12 months, but differences between groups were no more demonstrable at 24 months. However, it is essential to note that REVIVED-BCIS2 excluded patients with limiting angina or recent acute coronary syndromes, and PCI is still an option in these contexts.

CABG vs. PCI in patients with multivessel coronary artery disease

CABG and PCI for patients with multivessel coronary disease have been compared in many studies with non-univocal results[10-13]. Recently, the long-term follow-up of the BEST trial, which compared multivessel PCI performed with everolimus-eluting stents vs. CABG in patients with multivessel coronary artery disease, has been published[14]. The study was prematurely terminated in 2013, as at that time, only 880 of the planned 1776 patients had been enrolled[15]. In the BEST trial last report, PCI and CABG groups showed no significant long-term difference in all-cause death, MI, or target-vessel revascularisation. These observations were in line with the earlier reports of the study[15]. However, after 11.8 years of follow-up, PCI, compared with CABG, was associated with an excess of spontaneous MI (7.1% vs. 3.8%) and repeated revascularisations (22.6% vs. 12.7%). Long-term mortality was similar between treatment groups (20.5% vs. 19.9%). Interestingly, the excess of strokes reported in patients treated with CABG in most previous studies was not apparent in the BEST trial.

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Finally, this study was conducted in South Korea, and its findings may not apply to Western Countries patients.

Physiology-guided CABG for patients with multivessel coronary artery disease

From the coronary functional point of view, we want to remember that a substudy from the FAME 3 trial assessed the impact of post-PCI fractional flow reserve (FFR) and intravascular imaging on patient and lesion outcomes[16]. As known, the results of FAME 3 indicated that FFR-guided PCI using current-generation drug-eluting stents did not meet the criteria for non-inferiority compared with CABG among patients with angiographic three-vessel disease[17]. In this new analysis, only 61% had FFR measured following PCI, which was not required by the study protocol (43% one-vessel, 42% two-vessel, 15% three-vessel). In patients evaluated with FFR after PCI, the median final FFR measurement was 0.89; in 10% of patients, FFR was ≤0.80, despite angiographically successful intervention. Furthermore, an abnormal FFR after PCI significantly predicted target vessel failure using a cut-off value of 0.88 at the vessel level and 0.85 at the patient level. Moreover, only 11.1% of patients had intravascular imaging following PCI. In the study, the rate of cardiac death, MI, and repeat revascularisation was similar among the patients who did and did not have intravascular imaging guidance.

Ultrasound-guided access for transfemoral coronary interventions

The need for ultrasound guidance for vascular access is a hot topic, made even more actual with the current decrease in femoral vascular access in favour of the transradial route for routine and urgent coronary interventions. However, attention has returned to femoral artery access because the rate of structural heart interventions is steeply increasing. UNIVERSAL, a multicentre randomized clinical trial that compared ultrasonography-guided femoral access vs. fluoroscopy-guided femoral access in patients undergoing coronary angiography or PCI via femoral access, showed no benefit in using ultrasonography as a guide[18]. However, the randomized population was not consecutive patients undergoing diagnostic angiography, as many cases at these centres were performed with transradial access. Instead, they were selected patients chosen for transfemoral access due to anatomic considerations related to the radial artery or operator preference. Access sheath sizes were nearly all 6F or 7F, and approximately half of the cases were performed by fellows in training, as the trial was conducted at academic medical institutions. The investigators found that ultrasonography-guided access did not significantly reduce the risk of their primary outcome (a composite of Bleeding Academic Research Consortium grade 2, 3, or 5, bleeding at 30 days, and major periprocedural vascular complications). However, ultrasonography-guided access did reduce the time to obtain access, the need for multiple attempts at arterial puncture, and the incidence of inadvertent venipuncture. In a prespecified, nonrandomized subset of patients treated with a vascular closure device placed via operator discretion, a group with a considerably higher rate of vascular complications and bleeding, ultrasonography-guidance was associated with a reduction in risk of the primary outcome (11.8% vs. 23.4%; odds ratio, 0.44; 95% CI, 0.23-0.82). It is worth noting that the ultrasonography group in UNIVERSAL had a higher first-pass success rate and that, as stated before, very few patients with large-bore access were included in this study. A more significant benefit might have been observed in this setting with routine ultrasonography guidance. Until more evidence emerges or a meta-analysis is published that combines the data from the UNIVERSAL trial with data from other trials, it seems reasonable to use ultrasound-guided access for the femoral artery for coronary angiography and intervention and for large-bore vascular access for mechanical circulatory support and structural heart intervention.

Novel evidence in transcatheter valvular interventions

Turning to degenerative mitral valve disease, a novel transcatheter edge-to-edge repair (TEER) system called PASCAL was evaluated in the CLASP IID trial[19]. The CLASP IID randomized trial is the first to evaluate the safety and effectiveness of the PASCAL system compared with the MitraClip system in patients with significant symptomatic degenerative mitral regurgitation (DMR). The researchers randomized 180 patients (mean age 81 years, 33% women) with DMR at high surgical risk (3+ or 4+ mitral regurgitation grade) to the PASCAL or MitraClip system. The trial demonstrated that the PASCAL system was non-inferior to the MitraClip system for the primary

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safety endpoint of major adverse events (cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, non-elective mitral valve reintervention for 30 days), occurring in 3.4% and 4.8% of the patient groups, respectively ($p<0.05$). Cardiovascular mortality occurred in 0.9% and 1.6% of the respective groups. Although CLASP IID was a non-inferiority trial, it will expand treatment options for patients with severe degenerative valve disease. Ongoing studies compare TEER with MitraClip versus surgical mitral valve repair in patients with degenerative MR. One of those studies, PRIMARY, is a superiority trial funded by the National Institutes of Health with a planned enrolment of 450 patients at all levels of surgical risk. The other study is REPAIR MR, a non-inferiority study testing MitraClip versus valve repair surgery in intermediate-risk DMR patients. At last, the CLASP IIF study is also ongoing. In that study, investigators compare PASCAL to MitraClip in patients with functional mitral regurgitation and high surgical risk.

Finally, moving to aortic valve disease, the PROTECTED TAVR trial with 3000 patients found that the routine use of intraprocedural cerebral embolic protection (CEP) did not reduce the primary outcome of risk of stroke within 72 hours among patients undergoing transfemoral TAVR for aortic stenosis (2.3% vs. 2.9% with control)[20]. However, although this was a negative trial, there was a significant reduction in the secondary outcome of disabling strokes in the CEP vs. control group (0.5% vs. 1.3%; $p<0.05$).

Table 1. P2022 most relevant studies in Interventional Cardiology

Study Name	Description	Population	Primary Endpoint	Result
REVIVED-BCIS2	PCI vs. OMT in patients with EF<35% and extensive CAD	700 pts 1:1 allocation	All-cause death or hospitalization for heart failure	No differences
BEST	Multivessel PCI performed with everolimus-eluting stents vs. CABG	880 pts 1:1 allocation	All-cause death, MI, or target-vessel revascularisation at 11.8 yrs	No differences
FAME 3 substudy	FFR and imaging after PCI in predicting TLF	757 pts from the PCI arm of the FAME 3 trial. 61% had FFR, 11.1% had imaging	TLF	FFR predicts TLF with the cutoff of 0.88. Imaging use did not affect TLF
UNIVERSAL	Ultrasonography-guided femoral access vs. fluoroscopy-guided femoral access in patients undergoing coronary angiography or PCI	621 pts 1:1 allocation	BARC grade 2, 3, or 5, bleeding at 30 days, and major periprocedural vascular complications	No differences
CLASP II	PASCAL vs. MitraClip in patients with significant symptomatic degenerative mitral regurgitation	180 pts 1:1 allocation	Cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, non-elective mitral valve reintervention for 30 days	Non inferiority
PROTECTED TAVR	Routine use of intraprocedural CEP in patients undergoing transfemoral TAVR for aortic stenosis	3000 pts 1:1 allocation	Stroke at 72 h	No differences

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Conclusions

In a nutshell, we can summarize some very important take home messages from the 2022 studies. First of all, treating coronary artery disease with PCI in patients with left ventricular dysfunction may not not reduce MACE, but only in patients with in very stable clinical setting, since we have no data in patients affected by limiting angina and recent ACS.

Secondly, CABG vs. PCI in patients with multivessel coronary artery disease is an ongoing debate, with new evidence that confirms what we should expect from clinical practice: more short-term adverse events in CABG and more long term adverse events in PCI. This means that we probably should consider at most patient age than other clinical variables in our decision-making process.

Moving to physiology, FFR measurement after PCI predicts target vessel failure with a cutoff that is different from the one commonly used to define a de novo critical stenosis. Interventionalist should be aware of this in order to change their view in their PCIs.

Talking about ultrasound-guided access for transfemoral interventions, use ultrasound-guided access for the femoral artery has confirmed its safety, especially in interventions that require large-bore vascular access, even if data about adverse clinical events are not significantly lower with this approach.

Finally, transcatheter edge-to-edge repair for degenerative mitral valve disease could be performed with the new PASCAL device as well as with the well-known Mitraclip, since its non-inferiority has been demonstrated. At last, CEP in TAVR did not demonstrate any superiority in reducing the primary endpoint, but we should keep in mind that a reduction in disabling strokes emerged with the use of CEP.

Indeed 2022 was a very prolific year in terms of new evidence in Interventional Cardiology, but, as always, we must stay hungry and be careful in turning these new data into our clinical practice.

Declarations of interest: none.

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REVIEW ARTICLE

From data to drugs: Harnessing machine learning in drug discovery - A review

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Abstract

Drug development is a rigorous process essential for improving patient outcomes. However, this complex endeavour requires significant investment and time. The integration of Machine Learning (ML) techniques in drug discovery can revolutionize the field by efficiently processing large amounts of data and accelerating the identification and development of potential drug candidates. This review highlights ML's impact across drug development stages, from design to clinical trials (CTs).

Recently, the availability of high-quality databases and the surge in data digitalization has promoted the development of several ML algorithms, which have proved to be effective in classifying outcomes based on multivariate relationships. Particularly, Deep Learning (DL) architectures such as feedforward networks, Recurrent Neural Networks (RNNs), Convolutional Neural Networks (CNNs), and Long Short-Term Memory (LSTM) neural networks, represent a subset of ML which has been gaining popularity because of its ability to emulate the human brain and handle more complex tasks, thus representing a paradigm shift in data analysis and prediction.

ML plays a vital role in virtual screening, de-novo drug design and drug repurposing. Virtual screening methods can rapidly screen large chemical libraries and identify promising candidates for further investigation. De-novo drug design involves the use of ML-based generative models to produce new chemical structures with desired properties. Drug repurposing aims to identify

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new therapeutic uses for existing drugs. Additionally, ML can improve the efficiency of CTs by addressing challenges related to patient enrolment, study design, and phase transition.

The integration of ML with high-quality datasets can significantly improve drug development process, thereby increasing efficiency and success rates. However, it is important to address issues related to data quality, preprocessing bias, molecular representation, and interpretation of results. Harnessing the power of AI can accelerate drug development, ultimately benefiting patients and the healthcare industry as a whole.

1. Introduction

Drug development is a complex and rigorous process that involves the discovery, design, testing and approval of new drugs for the treatment, prevention or management of diseases and health conditions. It is an important aspect of healthcare that is critical to improve patient outcomes and address unmet medical needs.

Due to its highest standards, drug development process is long and expensive, often lasting several years and requiring significant investment. Up to an amount close to 2.5 billion dollars and five to ten years may be required to pass from bench-side to market [1–4]. Furthermore, despite rigorous testing, not all drug candidates make it through all stages of development due to limited or no therapeutic efficacy in humans or unacceptable toxicity leading to treatment discontinuation. It has been estimated that only 59% of drugs evaluated in phase 3 trials ultimately secure final approval from the Food and Drug Administration (FDA), and astonishingly, when considering the phase 1 trials, a mere 13.8% of drugs entering this phase ultimately attain final regulatory approval [5].

In the realm of drug discovery, the integration of Artificial Intelligence (AI) holds immense potential in terms of improving the efficiency and success rate of drug development process. However, its success heavily relies on the availability of a high-quality databases. In recent years, the pharmaceutical sector, as many others, has witnessed a remarkable surge in data digitalization, revolutionizing the way information is handled. This exponential growth of digitized data presented a formidable challenge of effectively acquiring, scrutinizing, and analysing the vast knowledge available. The development of advanced IT infrastructure has facilitated the organization, and accessibility of these data through user-friendly and widely accessible online databases.

Given this background, AI has emerged as a powerful tool for efficiently managing vast amounts of data through enhanced automation. This capability had a profound impact on the field of drug discovery, resulting in a paradigm shift in the applications of AI techniques. Machine Learning (ML), in particular, has been extensively utilized to analyse clinical data, learn from a large number of examples, and make predictions about the behaviour of unexplored datasets. These advancements have revolutionized the landscape of drug discovery, enabling us to gain valuable insights and make informed decisions based on the power trained models [6].

In this Review, we will try to give a brief overview of how ML may have an impact on different phases of drug development, from drug design to Clinical Trials (CTs). Particularly, we will commence by delineating the requisite technical specifications and operational procedures inherent to ML. Subsequently, our focus will pivot towards a comprehensive exploration of Drug Discovery, starting with its foundation: chemical libraries; this segment will elucidate the storage of potential drug candidates and the pivotal role that AI plays in either facilitating compound screening or engendering novel ones. Following this, we will explore the realm of Drug Repurposing, an alternative approach to conventional new drug development, which can serve as a valuable strategy to address unmet medical needs. Lastly, we will conclude by delving into the latest stages of drug development, where we will discuss the various ways in which AI exerts its influence across different phases, steps, and prospects of CTs.

2. Machine Learning: technical bases

While AI finds extensive application within the biomedical sciences, it predominantly retains its character as a technical discipline grounded in fundamental informatics. In order to furnish readers with a navigational aid within this domain, we provided concise definitions of the most technically nuanced terms employed in this review in **Table 1**.

TABLE 1 - Brief definition of technical AI terms. **1/2**

Terminology	Description
Activation Function	A function used in neural networks that adds non-linearity to the network, enabling it to learn from more complex data.
Artificial Intelligence (AI)	The science of creating intelligent machines capable of performing tasks that typically require human intelligence.
American Standard Code for Information Interchange (ASCII)	Character encoding standard for electronic communication, which is commonly used to represent text in computers and other devices.
Autoencoder Neural Networks (AENs)	Neural networks used for data compression and feature learning, consisting of an encoder and a decoder.
Backpropagation	A method used in artificial neural networks to calculate the error contribution of each neuron after a batch of data is processed, going back from the output layer to the hidden and input layers.
Canonization algorithm	An algorithm used to transform data or structures into a standardized or canonical form, making them more easily comparable or searchable.
Convolutional Neural Network (CNN)	A type of deep learning model primarily used for analyzing visual imagery. It uses convolutional layers to filter inputs for useful information.
Deep Learning (DL)	A subset of ML that uses artificial neural networks with multiple layers (deep structures) to model and understand complex patterns.
Deep Neural Network	Neural networks with multiple hidden layers, allowing them to model complex relationships in data.
Feedforward Networks	A type of neural network where the information flow is unidirectional, moving forward from the input nodes to the output nodes without cycles or loops.
Generative Models (GMs)	ML or DL models used to generate synthetic data, upon being trained on real data and have learned how to optimally approximate them.
Gradient Descent	An optimization algorithm used to find the values of parameters that minimize a given function by iteratively moving in the direction of steepest descent.
Hidden layer	The neural network layers that usually stay in between of the input and output layers.
Kernel Density Estimation (KDE)	Non-parametric method used in statistics to estimate the probability density function of a random variable, through using a non- negative, kernel function, to smooth the data points and generate a continuous and smooth estimate of the underlying distribution.

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TABLE 1 - Brief definition of technical AI terms. **2/2**

Terminology	Description
Long Short-Term Memory (LSTM) Neural Networks	A special kind of RNN capable of learning long-term dependencies, widely used in tasks involving sequential data and timeseries.
Loss function	A function to measure how well the network is performing with respect to its given training sample and the expected output. It quantifies the disparity between the predicted and actual outcomes, which is what the model seeks to minimize during training.
Machine Learning (ML)	A branch of AI that enables systems to learn and improve from experience without being explicitly programmed.
One-Hot Encoding	A method for representing categorical data as binary vectors, with one element set to 1 and the others set to 0 to indicate the category.
Overfitting	A modeling error in ML which occurs when a function is too closely fit to a limited set of data points and may therefore fail to predict additional data reliably.
Perceptron	A simple type of artificial neuron or node in a neural network, often used as the building block for more complex networks.
Quantitative Structure-Activity Relationship (QSAR) models	Regression or classification models used in the chemical and biological sciences and engineering.
Random Forest (RF), Naive Bayesian (NB), Support Vector Machine (SVM)	ML algorithms used for classification and regression tasks, each with its unique advantages and disadvantages.
Recurrent Neural Networks (RNN)	A type of neural network designed to recognize patterns in sequences of data, such as text, genomes, handwriting, or the spoken word.
Regularization	A technique used in ML to prevent overfitting by adding an additional penalty term to the loss function.
Simplified Molecular Input Line Entry System (SMILE)	A specific line notation for describing the structure of chemical species using short ASCII strings.
Supervised Learning	A type of ML where the model learns from labeled training data and makes predictions based on that learned knowledge.
Underfitting	A situation in ML where a model cannot adequately capture the underlying structure of the data due to its simplicity.
Unsupervised Learning	A type of ML where the model identifies patterns in dataset without any pre-existing labels, often used for clustering and association tasks.

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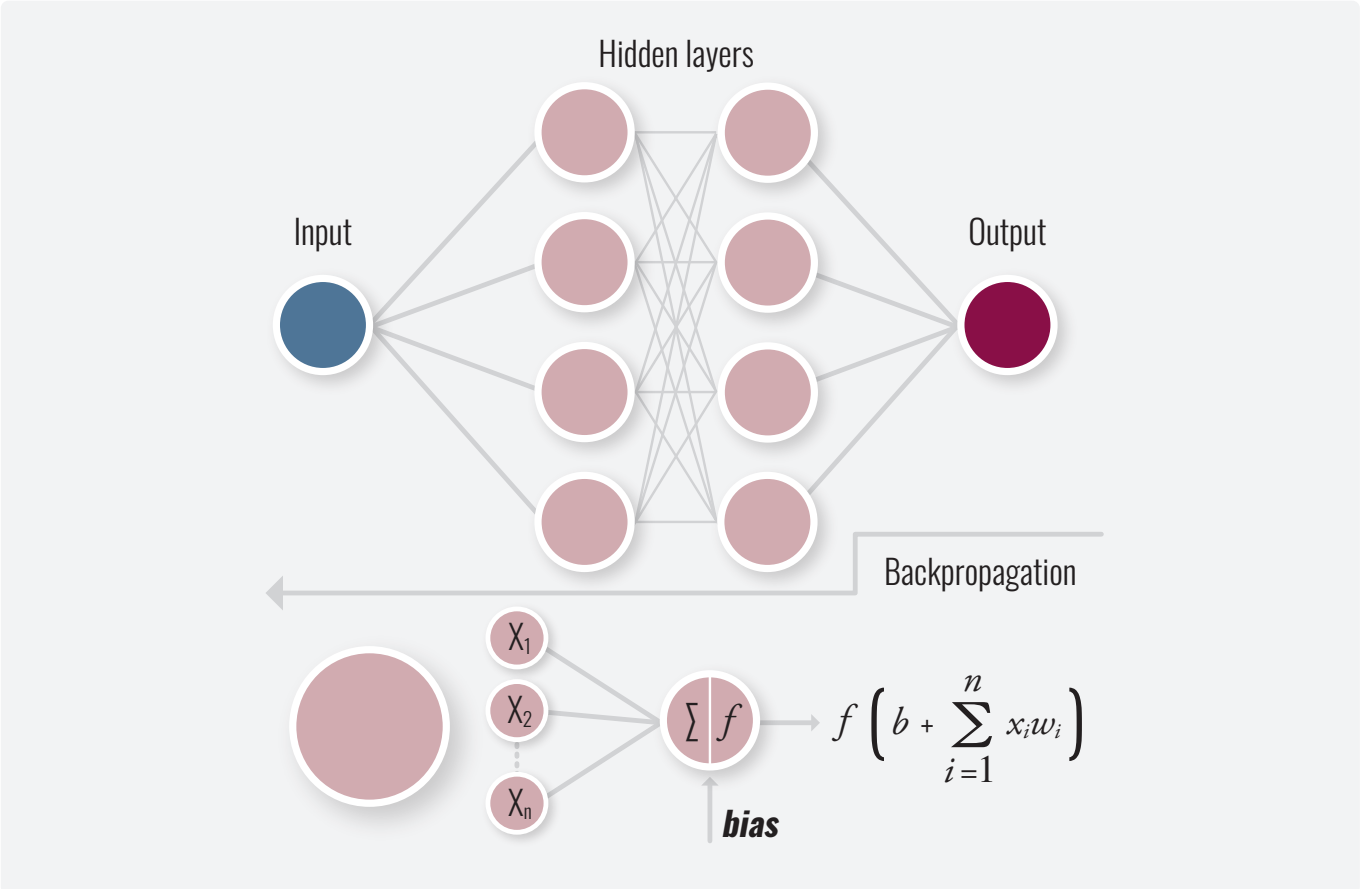
Among the diverse applications of AI, particular intrigue centers around the utilization of ML algorithms to analyse intricate datasets. Such algorithms are capable to perform pattern recognition in clinical imaging, extraction of fundamental insights from tabular data, and classification of selected outcomes by understanding multivariate relationships. The majority of AI techniques used in drug discovery can be divided into two primary categories: supervised learning and unsupervised learning. Unsupervised learning strategies are frequently employed for exploratory data analysis as they are valuable in identifying hidden patterns in data without pre-labelled information or facilitating data clustering. On the other hand, supervised learning involves training an algorithm with a set of input data to accurately predict specific outputs (such as class labels for classifiers or target values for quantitative outputs) for new, unseen data. In this field, supervised learning may be employed to understand molecular features associated with the bioactivity of compounds; in fact, by training the algorithm with labelled compounds that are either active or inactive, it becomes possible to predict the activity of new pharmacological agents based on their molecular characteristics [7].

ML encompasses several algorithms, most of which have been proven effective in the context of drug discovery. Random Forest (RF), Naive Bayesian (NB) and support vector machine (SVM) are few of the notable examples [8–10], which belong to the class of supervised learning methods. In recent times, Deep Learning (DL) has become popular amongst ML practitioners, due to its intrinsic capability to understand much more complex patterns and relationship. DL is a subset of ML where artificial neural networks with multiple hidden layers (hence the adjective 'deep') are used to model and understand complex patterns in datasets. The main objective of these models, usually referred to as Deep Neural Networks (DNNs) is to mimic the human brain structure, using multiple layers composed of a large number of computational units (perceptrons) **(Figure 1).**

FIGURE 1 - Schematics of a simple Deep Neural Network (DNN); in the bottom window, the mathematic operations of input weighting and output transformation performed by a single neuron (perceptron) are shown.



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Each layer is interconnected upon the previous layer and works towards minimizing the error between the expected and generated outputs, using backpropagation algorithms (e.g., gradient descent) to adjust weights and biases of the model function according to such error measurement. Through many iterations, these hidden parameters are updated and optimized, making the algorithm gradually more accurate. DL models are particularly effective when working with unstructured data such as images, audio, and text, as they become able to automatically learn feature hierarchies and extract most relevant information autonomously, eliminating the need for manual feature extraction which is necessary in traditional ML models. In terms of capability, DL mostly outperform conventional ML algorithms when dealing with complex, heterogeneous data, which is often the case in the domain of healthcare. However, DL models usually relies on large volume of data and their cognitive processes may be difficult to interpret, while other ML models (e.g. decision trees, clustering algorithms) may provide better accuracy when limited data is available (or in particular situations where they are more suitable for solving specific problems).

DNNs may be structured using different architectures, providing flexibility and adaptability to handle complex scenarios. Notably, feedforward networks have been widely used as they bear the simplest layout, being based on forwarding data from input to output in a streamlined manner. On the other hand, deep convolutional neural networks (CNNs) bear layers that are only locally (rather than globally) connected to the next hidden layer, allowing to perform convolutional transformation to hierarchically compose simple local features into complex models. Another interesting architecture is represented by recurrent neural networks (RNNs), evolving through a series of repeating modules of subnetworks. These loops are suitable to analyse dynamic changes over time where persistent information is needed throughout many iterative cycles. Long short-term memory (LSTM) neural networks are a special kind of RNN, widely applied for their capability of learning long-term dependencies from timeseries data. Data clustering with unsupervised learning is whereas carried out using autoencoder neural networks (AENs), which apply backpropagation with the purpose of dimension reduction, aiming at preserving most relevant variables while removing non-essential information. Some examples of the remarkable performance of DNNs in image recognition and classification tasks are reported in literature. Esteva and co-workers [11] developed a model that could perform skin cancer detection with an accuracy comparable to dermatologists, while Gulshan and his group [12] have used retinal images to train a model capable of detecting diabetic retinopathy in a fast and reliable fashion. Other notable examples are DL models that have been developed to predict the risk of various diseases using electronic health records and patient data, such as those developed by Houssein et al. [13] to predict the onset of cardiovascular events using electronic health records, achieving better accuracy compared to traditional models.

In the field of drug discovery, small drugs are designed by modulating the biological activity according to a specific molecular target. The identification of such target must be supported by a plausible therapeutic hypothesis, often related to a desired modulation of the disease state. Upon identifying the optimal target, the selection has to be validated using physiologically relevant ex vivo and in vivo models (target validation). Nowadays, biological research has produced an astonishing amount of data, including human genomics and proteomic, tabular clinical data and high-content imaging of patients. With the advent of ML, computational models have become more sophisticated and able to discern multivariate correlation patterns within highly dimensional datasets. An interesting example of ML in drug discovery is the use of random forest models to predict drug activity against cancer cells based on minimal genomic information and chemical properties[14]. These models have achieved sensitivities and specificities of around 87%, yielding an area under the receiver operating characteristic curve equal to 0.941. They also develop regression models to predict log (IC 50) values of compounds for cancer cells, achieving a Pearson correlation coefficient of 0.86 for cross-validation and up to 0.65–0.73 against blind test sets. In another study, random forest models were used for drug–target interaction prediction via Kullback–Leibler divergence[15]. This method uses E3FP three-dimensional (3D) molecular fingerprints of drugs as a molecular representation, allowing the computation of 3D similarities between ligands within each target (Q–Q matrix) to identify the uniqueness of pharmacological targets. The 3D similarity matrices are transformed into probability density functions via

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Kernel Density Estimation (KDE) as a nonparametric estimation, successfully predicting Drug-Target Interactions (DTIs) for representative 17 targets (mean accuracy: 0.882, out-of-bag score estimate: 0.876, ROC AUC: 0.990).

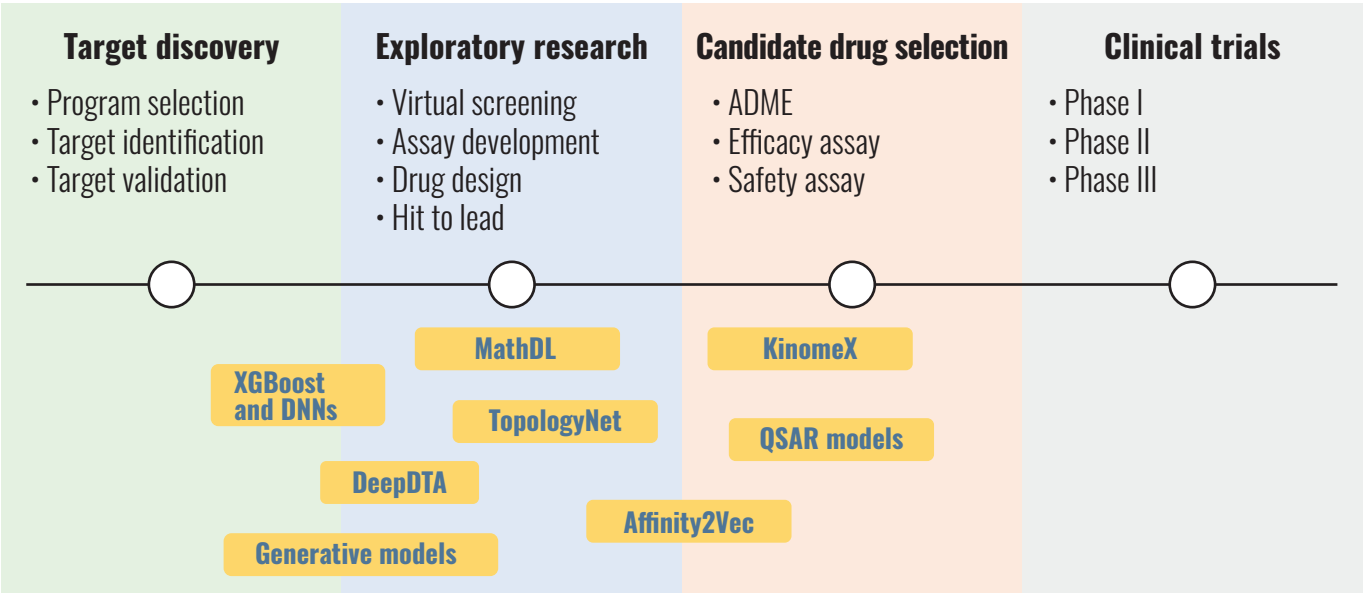
However, either by using DL or other ML methods one must account for considerable drawbacks due to the diversity and uncertainty of the data used as input feed. One clear example is represented by the data scale when considered across multiple variables, leading to a strong necessity to standardize data based on selected criteria. Data pre-processing has a deep influence on the ML outcome and overall performance of the trained model, adding further bias and deviations in the dataset. As the collection of data in the field of drug development can involve millions of compounds, traditional ML tools might not be able to deal with such abundant scale and complexity.

3. Drug Discovery

Drug discovery is a complex and expensive process that involves identifying and developing new drugs to treat medical conditions. The drug development process often begins with extensive research in pharmaceutical sciences. The goal of this step is to identify potential therapeutic targets associated with a particular disease or condition. Once a potential drug candidate is identified, it undergoes preclinical testing in laboratory settings and animal models to evaluate its safety, efficacy, pharmacokinetic and pharmacodynamic profiles. If preclinical studies yield positive results, the drug candidate enters three phases of CTs with an increasing number of participants. In summary, Phase 1 trials often mark the first human testing of a new drug, primarily focusing on establishing safety, tolerability, and appropriate dosage levels for subsequent phases. Phase 2 trials are designed to assess the treatment's effectiveness and safety within a larger group of patients with the specific medical condition of interest. Finally, Phase 3 trials, conducted on a large scale, aim to validate the medication's efficacy, monitor potential side effects, and compare it to established standard treatments or a placebo in a diverse and extensive patient population.

Once these steps are successfully completed, drug developers collect all preclinical and CT data and submit them to regulatory authorities, which ensure that the drug's benefits outweigh its risks and meet strict safety and efficacy standards. Eventually, upon approving the medicine, it can be marketed and made available to healthcare professionals and patients. DL methodologies are able to assist drug design by predicting optimal molecules from previously learned relationship amongst large datasets that may include chemical structures, biological activities, pharmacokinetics, and toxicological profiles. Deep models can optimize every step involved in the long process of drug discovery, from the identification of target to the analysis of CTs data. **(Figure 2).**

FIGURE 2 - Drug discovery phases and Deep Learning models which may be used.



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While DL methods have shown outstanding potential in the domain of drug discovery, traditional ML models may still hold an advantage in certain research scenarios. For instance, decision trees are frequently employed in drug discovery due to their interpretability [16,17]. They can be utilized to identify crucial features that contribute to a drug's effectiveness. The branches of the tree can provide insights into the decision-making process, such as "if a drug has feature X and Y, it is likely to be effective" [16,17]. Moreover, ML models require significantly less training data compared to neural networks and are often less computationally demanding than DL methods [16]. Support Vector Machines (SVMs), for example, have been used to predict drug toxicity with limited data[18]. Logistic regression, a relatively simple and computationally efficient ML model, can be used for binary classification problems in drug discovery, such as predicting whether a compound will be active or inactive against a specific biological target [19].

Usually, datasets available for drug development in pharmaceutical companies include millions of compounds. Quantitative structure-activity relationship (QSAR)-based computational model can easily predict large numbers of compounds or simple physicochemical parameters, but their accuracy may vary when predicting complex biological properties, such as the efficacy and adverse effects of drugs. In addition, QSAR-based models also suffer from small training sets, experimental data error in the latter and lack of experimental validations. In 2012, Merck supported a QSAR ML challenge to endorse the deployment of DL methodologies in the drug discovery process, showing that those are significantly better at predicting absorption, distribution, metabolism, excretion, and toxicity (ADMET) of drug candidates, when compared to traditional ML methods [20].

As it has been mentioned earlier in this review, DL methodologies have shown great promise in the field of drug discovery. However, their implementation is not without challenges. One of the primary hurdles is the requirement for large and diverse datasets of high-quality chemical and biological data. In drug discovery, obtaining such data can be challenging due to issues such as experimental noise, missing values, data imbalance, data heterogeneity, and data privacy [21]. Another challenge lies in the interpretability of DL models. Often considered as black boxes, these models do not provide much insight into how they make predictions or what features they use [21,22]. This can limit their usefulness in drug discovery, where understanding the molecular mechanisms and the reasoning behind predictions is crucial for generating new hypotheses and designing new experiments. DL models can sometimes be prone to overfitting, a phenomenon where the model learns the training data too well, to the point that it performs poorly when presented with new or unseen data. This can lead to false positives or false negatives in drug discovery, where the chemical space is extremely vast and complex, and many molecules share similar physicochemical properties. Overfitting is directly opposed to underfitting, where the model is not powerful enough to minimize the error between true labels and predicted labels and therefor extract any useful information from the given data. Lastly, DL models need to be rigorously validated and evaluated using appropriate metrics and methods to ensure their predictive power and applicability domain. However, there is no consensus on how to best validate and evaluate DL models in drug discovery, especially when dealing with imbalanced or sparse data, multiple targets or tasks, or novel compounds [23].

3.1 Chemical libraries

Chemical libraries are repositories of molecules which are largely used in chemical industries and academic centres. Molecules included in the database are atomized into several descriptors, such as structural and physicochemical ones, providing information on chemical structure, molecular weight, atoms and bonds type, as well as solubility and acidity/basicity. Depending on the library, the wealth of information about each molecule may include pharmacokinetics (how the compound is absorbed, distributed, metabolized, and excreted by the body), pharmacodynamics (its biochemical and physiological effects), and toxicology. Other potential features could be the synthetic accessibility of the molecule (how easy it is to synthesize), commercial availability, or even its predicted activity against specific biological targets. Moreover, with the advancement of cheminformatics, new methods for molecular description have been developed. These include various 2D and 3D molecular descriptors, such as path-based fingerprints, extended-connectivity fingerprints, 2D pharmacophore fingerprints and extended 3D fingerprints [24].

Data for pharmacological features are manually extracted

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from published literature and are routinely updated. Moreover, regulatory agency documents are periodically checked for schedule of administration, indications and warnings of drugs. At present, some compound databases are available online and extensively used in DL (i.e., PubChem, ChEMBL), containing over 105 million compound candidates [25,26]. Such databases have integrated advanced information regarding drugs biological activity, most in the form of QSAR descriptors [27]. **(Table 2)**

TABLE 2 - Molecular descriptors available in chemical libraries based on their dimensionality [27].

Descriptor Dimensions	Properties
NON-DIMENSIONAL	• Molecular weight • Atom number • Atom-type count
1D DESCRIPTORS	• Functional groups • Substituent atoms
2D DESCRIPTORS	• Molecular topology • Connectivity bonds
3D DESCRIPTORS	• Steric properties • Molecular geometry • Surface area and volume • Binding site properties

In particular, the ChEMBL database maintained by the European Bioinformatics Institute (EBI) of the European Molecular Biology Laboratory (EMBL), contains 1.6 million distinct compounds, 14 million bioactivities, 11 thousand biological targets, and other related data. Furthermore, it is equipped with toolkits for data mining [28], including tailored resources for specific tasks, as for example Kinase SARfari (chemogenomics workbench focused on kinases) or ADME SARfari (tool for predicting and comparing cross-species ADME targets). Another notable database is the QM9, which is a widely used in the field of computational chemistry and includes quantum mechanical calculations for a diverse set of small organic molecules [29]. The QM9 dataset provides important molecular properties such as atomization energies, equilibrium geometries, dipole moments, and other complex molecular parameters. It has been used for the development and validation of ML models for molecular property prediction and drug discovery.

While these databases may comprise millions of different molecules, they are far from covering the entire chemical space. As a matter of fact, both empirical and simulated molecules may exist in available databases. In this context, empirical molecules refer to those that have been experimentally observed and characterized in the laboratory, which data is derived from actual experimental results, and their properties and behaviours are known based on empirical evidence. On the other hand, simulated molecules are those that have been predicted or generated using computer simulations, such as molecular dynamics simulations using mathematical models and algorithms to predict the properties and effects of molecules according to their

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atomic composition and structure. Predicted molecules are often collected in designated databases known as virtual libraries. Such libraries may be divided in static and dynamic [30]. Static libraries aim at enumerating all possible virtual molecules that may exist in a specific field. As an example, GDB-17 report about 116 billion virtual organic molecules [31]. Other libraries, such as ZINC, has far less compounds (around 22 million) but are free, focused on ready-made molecules and provide three- dimensional conformations, therefore are widely used in ligand- and structure-based virtual screening studies [32]. Aiming at completeness and performing a screening afterward as in static libraries may be good strategies to systematically screen chemical space; however, it must be considered that libraries by definition may not be completed, and the largest the library, the most difficult it becomes to perform a screening. For this reason, dynamic libraries have been developed, which may be seen as an algorithm capable of investigating only the chemical space around molecules of user interest, thus enabling fastest and more efficient screening. A common example is PINGUI, a free tool which identifies reactive site of a molecule and recombines resulting fragments as building blocks to complement the core fragment and generating a tailored chemical space defined by the scientist [33]. Both types of libraries have pros and cons and should be used combinedly. Future challenges will involve how to store and screen such a large amount of data and how to make them available to a larger audience for research purpose [30].

3.2 Virtual Screening of molecules

In the last decades, virtual screening (VS) has emerged as a more efficient way to physical screening; it consists **of** a computational screening of large libraries of molecules which compared biochemical properties, such as structure similarity, and gave a rank of most promising drugs [34,35]. Overall, VS strategies may be divided in two groups:

1. ligand-based methods: starting from an already existing input molecule, these methods try to find similar molecules in an extensive chemical library basing on atoms types and reciprocal connection and three-dimensional configuration.
2. structure-based methods: in this case, the search in chemical libraries aims at finding pharmacological agents that may fit a known binding site. Since these latter methods do not require an input compound, they are more useful than ligand-based ones in case of biological target with no binders available yet. For the same reason, as a drawback, structure-based virtual screening may be less accurate [35].

Ligand-based methods have revolutionized the field of drug discovery by delivering new drug candidates more quickly and at a lower cost. These methods allow for rapid VS of molecules, utilizing pharmacophoric techniques and alignment methods based on ligand shape and electrostatic similarity. Such techniques have proven their efficiency in identifying novel potentially active compounds [36,37]. On the other hand, structure-based techniques have unveiled a plethora of potential drug targets. These techniques facilitate enhanced meticulous target identification and validation, thereby reducing efficacy-related drug attrition. Furthermore, once the crystal structure of a target is obtained through structural biology techniques such as X-ray crystallography, Nuclear Magnetic Resonance (NMR), neutron crystallography (NC), cryo-Electron Microscopy (cryo-EM), and mass spectrometry (MS) among others, researchers can swiftly establish the structure-activity relationship of the compound. This accelerates the process and reduces the number and time of compound synthesis [38,39].

Overall, VS allows for a fast screening of large chemical libraries going beyond empirical screening capabilities and pragmatically providing lists of likely candidates for further studies. However, some challenges must still be faced. First, spatial conformation of molecules is not fixed: molecular flexibility in aqueous environment and dynamic structure of receptors make it far more complex to establish ligand-receptor absolute binding energies and energetically accessible conformations of receptors; this process may require relevant resources in terms of time and CPU power [34,35]. Second, although efficient, VS may still make mistakes by incorrectly missing a true efficacy of an agent or, more importantly, by anticipating activity of an inactive drug. In drug development, even a minimal false positive rate of VS may lead to a large number of compounds tested, with both an increase of expenses for testing and an obscuration of the signal of truly active molecules [35,40].

DL methods play a vital role in evaluating physicochemical properties, target affinity, and pharmacokinetic (PK) profiles of potential drug candidates, becoming a valuable tool to speed up the drug discovery process. In particular, DTI prediction has been of great help for drug repositioning

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and virtual drug screening. Binding affinity prediction has been explored using DL methods. One of the biggest challenges when manipulating the complex molecular data consist in the identification of the most optimal encoding method. Molecules are often encoded according to the Simplified Molecular Input Line Entry System (SMILES), which represent and efficient way of storing information from the molecular graph using string characters [41]. SMILES allows for the linearization of the molecular graph by enumerating the nodes and edges on the bases of a certain path. However, it is affected by the randomness attributed to the selection of the starting atom in the 2D graph, meaning that multiple SMILES may exist for one molecule. For example, the canonical SMILE notations for water and ethanol are O and CCO, respectively. [42,43] SMILES are usually taken in consideration as they may be standardized through canonization algorithm. This latter is a procedure that generates a unique and unambiguous representation of a molecule, usually by assigning a priority to each atom based on its connectivity, atomic number, chirality, and other properties, and then generating a SMILES string that follows the priority order. While there are different canonization algorithms, they all aim to ensure that the same molecule always has the same canonical SMILES string. Another method is represented by labelling and "one hot encoding", a process by which categorical variables are converted into a new categorical feature with binary values assigned (1 if present or 0 if absent), allowing to represent each integer value as a binary vector [44].

Several DL methods have shown to outperform conventional ML approaches, due to their generally better capability of handling high-dimensional data that is particularly useful in domains with large datasets including hundreds of features. DL methods are also largely superior at pattern recognition, which proves to be extremely helpful when discerning patterns and discriminative features in molecules with complex structure and topology. In some cases, DL models are enhanced by using algorithms that have been widely validated in conventional ML, as is the case of Cheng Chen and co-workers, who have applied XGBoost algorithm together with multi-layered DNNs to build a drug-target interactions predictor, achieving an accuracy above 98% and outclassing other state-of- the-art prediction systems [45]. A real-life example is high-performance DL models is brought by the Affinity2Vec, a drug-target binding affinity prediction model based on representation learning [46].

Another network-based approach is DeepDTA [47], which uses a heterogeneous graph attention (HGAT) model coupled with bidirectional ConvLSTM to learn topological information of compound molecules and modelling spatial-sequential information based on the molecular SMILES sequences. This is yet a further examples of superior deep networks performances, due to the ability to learn hierarchical representations. This means that they can learn multiple levels of abstraction from data, where lower layers hold information about general molecular shape and topology, while deeper layers may gain insight on more complex physicochemical properties. Beside the model layout, other approaches may be undertaken to improve the capability of DL; such is the case of two models, namely MathDL and TopologyNet, which make use of algebraic topology to identify interactions between protein and ligand. In particular, MathDL [48] exploited advanced mathematical techniques such as graph theory to encode the physicochemical interactions into lower-dimensional rotational and translational invariant representations. TopologyNet [49] is created as an ensemble of multi-channel topological CNNs to represent the protein-ligand complex geometry through 1D topological invariants for affinity prediction and protein mutation. Finally, some DL applications have been focused on specific segments of the drugs chemical space, such is the case of KinomeX. The latter is an online platform to predict polypharmacology effects of kinases solely based on their chemical structures. A multi-task DNN model trained with over 140 000 bioactivity data points for 391 kinases carries out predictions for the users, enabling them to create a comprehensive kinases interaction network for designing novel chemical modulators [50].

3.3 De Novo Drug Design

It has been estimated that the total number of organic compound that may potentially be synthesized ranges from 10^{30} to 10^{60} [35]. Searching for a potentially useful drug amidst this vast compound space is akin to looking for a needle in a haystack for pharmaceutical industries, as it accounts for a large amount of money and time. For this reason, rational de novo design approach has always been used. De novo drug design essentially involves the creation of new chemical structures with specific desired properties, such as a particular biological response.

Traditionally, computational methods proceeded one

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molecular fragment at a time to highlight worse or better biochemical properties of the new drug. This process may obviously benefit from automated methods for constructing these novel structures. This is the reason why ML may be extremely helpful in this field as well and Generative Models (GMs) have been proposed. A generative model is a ML algorithm which may retrieve data of existing chemical compounds to identify patterns and chemistry rules which may be employed to generate new molecules [51]. Technically, GMs are made of three parts linked by a neural network: first, an encoding module converts a set of molecules into a continuous vectorized representation; then a decoding module reconstructs the continuous vector representation back into a molecule; lastly, a predictive module computes one or multiple properties for vectors derived from the continuous representation [35]. Gomez-Bombarelli and colleagues were among the first to propose this new method based on encoding of compounds and showing good prediction power [52].

The choice of molecular representation to be presented to the encoder significantly influences the learning process of the model, determining how molecular information is acquired. There are three primary types of representations: 3D (e.g., coordinate-based), two-dimensional (e.g., molecular graphs) and one-dimensional. The commonly used 1D representation is SMILES notation, which is particularly suitable for neural network architectures designed for language processing [7]. For example, a generative neural network trained on SMILES was recently developed to de novo design a ligand for nuclear receptor related 1 (Nurr1), a transcription factor involved in neurodegenerative disease pathways; these strategies led to the synthesis of two candidates with desired activity, one of which with a notable potency, even if this network was trained with a relatively limited number of molecules due to the lack of active drugs in this setting [53].

However, ML models often struggle to fully comprehend the intricacies of SMILES grammar, resulting in the generation of invalid SMILES that cannot be translated into meaningful molecular structures; therefore, other strategies have been proposed [54]. Similarly, considering molecular 3D structure may represent an issue, as different forcefields and interactions are involved in determining spatial conformation. To address this challenge, recent efforts have focused on training 3D generative models using extensive sets of conformers. For example, the geometric ensemble of molecules (GEOM) comprises over 37 million molecular conformations for about half million molecules [55].

3.4 Chemical synthesis of drugs

Not only must new drugs be designed, but they have also to be effectively synthesized; only a relatively small number of chemical reactions have been shown to be used in recent years and few have been introduced compared to 40 years ago. On the one hand, these commonly used reactions are reliable and have led to a wide range of commercially available building blocks that can be effectively exploited. On the other, despite the growth in synthesized drugs, the limited variety of reactions used has led to certain regions of the chemical space being densely populated with structurally similar molecules, while other regions remain unexplored [56].

Recent developments include the use of AI to process large databases of organic reactions and propose new synthetic pathways. This process consists of two activities: research and reaction prediction. The research involves identifying a series of chemical reactions to form a retrosynthetic pathway between a target compound and starting materials. Afterwards, reaction prediction determines the feasibility of those reactions basing on the context [51,57].

Two approaches may be used to investigate steps of organic synthesis: template-based and template-free methods. Template-based methods use hand-coded reaction templates to describe determined steps of bond formation among atoms: they have been widely used for decades, but can be computationally expensive and limited by the quality of the templates [58]. More recently, template-free methods have been introduced: they use neural networks to learn the relationship between reactants and products. In particular, neural networks consider chemical blocks as a sequence of characters, such as in the SMILES strings. After a proper training on a large database of chemical compounds, the neural network tries to generate reactants given the proposed products, thus suggesting new chemical reactions [59]. Additionally, neural networks may be trained by associating a large number of molecules to known originating reactions in order to predict the probability of a further reaction to produce the desired product [60]. However, assessing the feasibility of unprecedented reactions can be difficult, as the same reaction in different conditions (i.e. time, temperature and catalysts) may lead to different yields; therefore, it may still takes resources to be validated [51].

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4. Drug repurposing

Drug repurposing is the process of identifying new therapeutic applications for existing drugs. This strategy is achievable as drugs may have several targets, which may induce different effects according to contexts and diseases. Drug repositioning has various advantages over traditional drug development, including shorter development times and lower costs, given that the safety and pharmacokinetic profile of the drugs have already been established [61].

However, finding novel uses for currently available medications is a difficult endeavour as it necessitates a thorough comprehension of the drug's mechanism of action as well as the underlying molecular pathways of the condition of interest. AI has emerged as a viable technique for drug repurposing, as it can scan vast volumes of data on pharmacological characteristics and disease pathways in order to find new therapeutic targets and indications. As an example, drug repositioning strategies were proposed in the first phases of Coronavirus disease (COVID-19) pandemics. In this setting, challenges in drug repurposing included limitations of preclinical assays, suboptimal CT designs, lack of appropriate clinical endpoints, and the absence of reproducible preclinical animal models. ML was thought to provide in the shortest time pharmacological agents to treat the disease while bypassing traditional development steps required for new drugs [62]. Similarly, an integrative deep network that combined multiple relationships and leveraged a vast amount of information embedded as vectors from the PubMed and DrugBank databases was proposed [63]. 41 drugs, including dexamethasone and indomethacin, were predicted to have repurposing potential as therapeutic agents against for treating SARS-CoV-2.

Furthermore, several AI-based drug repurposing methods have been developed, including ML algorithms, network-based approaches, and natural language processing methods. These strategies typically involve the integration of multiple data sources and the use of advanced statistical and computational techniques to identify potential drug-disease associations. One of the main benefits of AI-based drug repurposing is the ability to integrate multiple data sources with Real-World data, such as electronic health records and CT data, to identify new drug-disease associations that might not be immediately obvious using traditional approaches and statistical methods which are limited in handling a substantial amount of data. Liu and colleagues proposed a framework for screening of on-market drug candidates by retrospectively analysing Real-World data [64]. In particular, they emulated randomised CTs to systematically evaluate drug efficacy on a panel of diseases; moreover, DL techniques were used to control for confounders in real-world data through a propensity score estimation model. Additionally, they provide an example which demonstrates the effectiveness of the proposed computational drug repurposing framework in identifying potential drug candidates with beneficial effects on disease outcomes for coronary artery disease patients, even outreaching the performances of other existing pre-clinical drug repurposing methods. This new approach may be exploited whenever real RCTs are not available despite a large volume of observational data.

However, further progresses are required. Data and model harmonization are essential for the development of broadly applicable and interoperable computational tools for drug repositioning. Similarly, data security and privacy concerns must be addressed through careful consideration of the data lifecycle and the implementation of regulations and transparency [62].

5. Clinical Trials

CTs are the gold standard to prove efficacy of a drug and are required by regulatory agencies for releasing marketing authorisation. Although CTs require a large amount of time and resources to be performed, a positive result is not guaranteed even in case of a true effect of the drug; in fact, many pitfalls are described in terms of patients' enrolment, study design, trial conduction and phase transitions, which may lead to trial unsuccess. Recently, ML has been discussed as a way to overcome these problems and offering several opportunities for improving the efficiency of different trial process steps [65,66].

First, patients' enrolment is one of the major challenges in CT conduction. This is due to both complex protocol designs, which makes it difficult to include subjects and fully adhere to the conduction, and lack of interest of the patients. It has been shown that only 15% of CTs manage to entirely avoid patients dropout, while average dropout rates are about 30% [66]. Notably, a poor recruitment with a high number of dropouts may lead to trial discontinuation due to the inability to demonstrate the outcome. In this setting, ML algorithms can identify potential CT participants by analysing electronic health records, large datasets, and patient files. By more effectively identifying the right

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participants, they can help streamline the recruitment process and speed up trial enrolment, thus leading to faster and more reliable results [67]. Additionally, this may reduce early stopping of CTs due to insufficient patient enrolment or high rates of dropout. It has been suggested that AI may predict likelihood of dropouts from CT: this information may be used to focus effort on these patients to provide additional education to encourage longer participation [68,69].

Second, CT design may be optimized as well under different points of view. It has been shown that AI may simulate different scenarios according to trial design, sample size, randomization strategy, and statistical analysis plan and evaluate their likely outcomes [66]. Moreover, AI may even permit the substitution of control group with an artificial one in future: given a large amount and variety of data from each enrolled patient, AI might predict individual natural history and disease progression; in particular, this study design emulates the impact of placebo on virtual patients and compares it to the intervention group of RCT; by employing synthetic control arms, this approach ensures that all enrolled participants receive the experimental intervention, thereby addressing concerns related to treatment assignment and the potential for unblinding [69,70]. However, these strategies need to be fully validated in order to ensure an efficacy comparable with traditional trials.

Third, trial conduction may be improved as well. ML may provide real-time monitoring of patient data to ensure safety and efficacy parameters are met. Continuous data analysis might identify patterns, outliers, adverse events and treatment responses in a timely manner, thus enabling prompt intervention and improved patient safety. Non-stop monitoring may be further permitted by wearable devices which monitor patient's parameters 24 hours a day, thus reducing number of missing data points [71]. Even traditional tests performed during CTs may be affected: ML techniques can automate the evaluation of trial endpoints, such as analysis of radiographic images or pathology slides, thus reducing manual workload, and enabling more efficient data analysis. For instance, Erdaw et al. developed a model to accurately make diagnosis of COVID-19 using digital chest X-ray image. Remarkably, the model achieves an accuracy of over 97% [72].

Therefore, by integrating patients' characteristics, historical data, biomarkers and treatment outcomes, ML may help optimize treatment options by identifying patient subgroups that may respond differently to interventions; this may be relevant considering the increasing interest raised by personalised medicine in order to tailor pharmacological treatment to each patients' characteristics [73].

Lastly, ML can be employed to assess the likelihood of success during CT phase transitions. This aspect holds great importance considering that only one out of every five drugs that enter phase 1 CTs ultimately receives marketing authorization [66]. Specific algorithms have shown an average accuracy of approximately 80% in predicting the outcome of these transitions. This capability can offer advantages to both trialists, who can utilize the information to refine protocol designs, and pharmaceutical industries, which can save resources and allocate budgets more effectively [74].

6. Conclusions

ML methodologies can have a deep impact on drug development; DL, especially through the use of generative models, has demonstrated significant advancements in drug design and investigating protein-ligand binding processes, leading to a renewed enthusiasm in the field.

Despite progress made in recent years, at the moment GMs are unlikely to automatically produce drug candidates with optimal properties due to the complexity of molecular interactions. In fact, these interactions hinge on the three-dimensional conformation of receptors, which, in turn, relies both on the structural composition of aminoacidic chain, and environmental factors, including pH, temperature and oxidation. These factors influence molecular flexibility, receptor affinity, and other features that algorithms may not consistently predict automatically in every instance.

For these reasons, the input of human expertise continues to be crucial. Therefore, further advancements in next years are required in terms of:

1. data curation and quality,
2. appropriate model validation and ways to handling uncertainty in predictions;
3. improving data accessibility, ensuring clearer interpretation, better readability, and the potential for reuse, with the aim of reducing resources waste, accelerating innovation and providing new drugs for unmet clinical needs.

Automation and combining multiple approaches - generative, predictive, synthesis planning - will surely be promising research directions. Another challenge is represented by performance evaluation: comparing

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experimentally determined and predicted values for physical properties or biological activity may represent a benchmark for ML models evaluation; additionally, comparison among techniques should be performed as well, in order to minimise costs and maximise results.

The final phases of drug development have also benefited from these new techniques. Incorporating AI in CTs holds great promise, as it is predicted to advance medical research and make it more sustainable. Continuous efforts have been made to investigate the potential of AI in order to conduct more efficient and profitable trials. To fully validate these methods, however, much more research is needed. Additionally, as there is still a lack of specific ethical and regulatory guidance focused on AI's use in CTs, adoption of digital transformation will likely be cautious and slow. Sponsors, investigators, and regulators may successfully tackle all of these issues by working together closely and using a patient-centered, ethical strategy.

In conclusion, a considerable amount of effort is still needed to fully integrate AI algorithms into standard drug discovery processes. However, this emerging technology holds the potential to substantially enhance drug development, even in areas where unmet medical needs persist. In this context, there is a reasonable expectation that ML may become a reliable tool to effectively address the challenges that both basic and clinical researchers currently have encountered for years.

Conflict of Interest

The authors declare no competing interests.

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BRIEF ARTICLE

BLS-D, I'm ready to perform CPR!

Parma University project

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Abstract: Since 2021, the training of newly licensed physicians (NLPs) has become obligatory in Italian universities. The Italian Society of Medicine and scientific Divulgation (SIMED) proposed a training project, including Basic Life Support Defibrillation (BLS-D), to the lecturers of Medicine and Surgery department at the University of Parma, assisted by the student representatives of the Camici In Movimento (CIM) group.

Methods: Before the course, a survey was submitted to students to understand their theoretical knowledge and ability to start Cardio-Pulmonary Resuscitation (CPR) manoeuvres.

Results: 52 questionnaires were collected. 23% of students didn't show sufficient theoretical knowledge. People who had completed an eight-hour BLS-D course, according to guidelines, reported feeling more confident managing Cardiovascular Arrest (CA) (OR 32.9; 95% CI 5.6-193.8 p<0.01) than those who had not. Students who had witnessed a CA showed more confidence in managing a future CA (OR 8.3; CI 95% 1.9-36.0 p<0.01). 8 subjects (15.4%) had completed a BLS-D course and had managed a CA.

Conclusions: Medical students, who had already attended an 8 hours BLS-D course and witnessed a CA, proved to be more likely to handle cardiac arrest. The training course should, therefore, be included among the mandatory courses planned for a bachelor's degree.

Keywords: Cardiopulmonary Resuscitation, (Education, Medical, Undergraduate), Italy, Surveys and Questionnaires, Public Health

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Introduction

From 2021 the medical degree has become qualifying for all students who complete their studies. In this context, newly licensed physicians, i.e. qualified for the profession for less than 12 months, have to show a rapid level of autonomy, greater than that of doctors who carried out a specific professional qualification course, since they are immediately committed to working in the Italian National Health Service (SSN) [1-2].

Furthermore, the COVID-19 pandemic, which has significantly affected Italy [3], has highlighted the chronic shortage of healthcare professionals and shown the importance and value of NLPs [2]. The assessment of the autonomy degree and the training needs of the healthcare professionals is a very important issue, which universities would have to develop with specific courses. For this reason, the Italian Society of Medicine and scientific Divulgation (SIMED) has developed a specific course. The course was born by the analysis of this population's training needs [1-2] and the understanding of the satisfaction degree of the learners, and the clinical capacity deriving from the monothematic practical courses [4].

Through the analyses conducted by SIMED, we have highlighted the training shortcomings on various topics [2], but we have also shown that the training request is more concentrated on practical-clinical training [5], [6].

Moreover, we have registered greater autonomy in the management of clinical cases in certain settings, such as during the Emergency Room (ER) shift [5] in subjects trained through a specific education, which, despite this, is still deficient [6]. The training projects of the outgoing guidance are dispersed in various universities and do not present clear national guidelines [7]. This is a very relevant topic, in fact, even now medical students during the last years of the degree course have shown a sub-optimal theoretical knowledge in emergency management [8]; training in specific topics or with advanced simulation still seems to be linked only to some postgraduate courses, such as anaesthesia or emergency medicine [9 - 10]. This vision remains short-sighted, as during the COVID-19 pandemic, and does not take into account the difficult settings which the NLPs may encounter, and in which the ability to manage an emergency can be central.

The ability of the NLPs to perform CPR is still lacking [11], as well as the ability to manage an emergency autonomously. During the COVID-19 emergency, the importance of training has been central [12] and new modalities have been developed [13]. Despite that, practical training remains crucial for the emergency management [14-15], because different factors may influence its failure [16]. Considered the importance of BLSD training for the NLPs, SIMED has organized an accredited course as an Elective Educational Activity in collaboration with the University of Parma, aimed at sixth year medical students. This course has been included in the educational curriculum of students enrolled in the sixth year of medicine for the 2022/23 academic year. Enrolments were opened on the University of Parma website and student representatives managed the enrolments.

Methods

The study design is a survey assigned to the students of the Extracurricular activities BLS-D course; it has been carried out according to the American Heart Association guidelines [17]. 54 students enrolled in the sixth year of medicine attended the course. The course was structured in groups according to the number of students: 4 groups of 12 students and 1 of 6 students. A 13-question questionnaire was distributed prior to the beginning of the course. The questionnaire was compiled before the start of the course. 10 minutes were guaranteed before the course to give all trainees the time to complete it. 2 of the questions were demographic (gender and age), 8 questions investigated theoretical knowledge (closed answer with 4 possible answers) and 3 (closed answer with dicotomic answers) were related to previous experience with Cardiac Arrest CA (having attended a course, having witnessed a CA or being prepared to undertake a CA). A score from 1 to 8 was assigned to the individual learner based on the number of correct answers. In the first 8 theoretical questions, it was possible to decide on one of the 4 answers for each question. Only one answer was correct, and one point was awarded for each correct answer. In this way, a score from 0 to 8 could be achieved depending on the number of correct answers.

The study was developed in line with the Declaration of

Helsinki and has been approved by the SIMED council. The anonymity of the students was ensured during the collection of the questionnaires by the SIMED instructors.
The course was carried out at the SimLab simulation center of the University of Parma.

Results

Of the 54 questionnaires distributed, only 52 were fully completed by the learners, all questionnaires was anonymous. The interviewed population had an average age of 26.2 (SD: 1.9), was composed of 33 (63.4%) female subjects and 19 (36.6%) male subjects. The mean score on theoretical knowledge was 5.6 (SD: 1.3). Of all the interviewees, 12 of them (42.3%) registered a score lower than 5, which is defined as insufficient. Comparing the population with insufficient theoretical knowledge (score lower than 6) with the population who registered sufficient theoretical score (score higher than or equal to 6), the self-reported safety in managing a CA did not change (OR 0.3; 95% CI 0.06-1.07 p=0.07).
Regarding previous experiences with cardiac arrest, 40 (76.9%) did not attend a BLS-D course of at least eight hours according to guidelines [18], one person did not answer, while the remaining 11 (20.0%) completed at least one course. Concerning CA, 40 (76.9%) learners did not witness a CA, 1 did not respond and 11 (20.0%) witnessed at least one CA. Finally, only 14 (27.0%) interviewees feel ready to manage an CA, while 1 did not respond and 37 (71.2%) do not feel ready.
Among the interviewed population, subjects who attended an eight-hour BLS-D course, according to guidelines, report feeling confident in managing a CA (OR 32.9; 95% CI 5.6-193.8 p<0.01). For those who witnessed a CA, the odd of managing a CA is higher (OR 8.3; CI 95% 1.9-36.0 p<0.01). As many as 8 subjects attended a BLS-D course and managed a CA, this figure represents the 15.4%.
The gender did not influence predisposition to manage a CA (OR 0.6; 95% CI 0.1-2.2 p=0.4).
At the end of the training course, performed according to American Heart Association guidelines, all 54 students successfully passed it, with adequate theoretical and practical scores.

Table 1. Percentage of correct answers to the questionnaire's questions.

Question	% of correct answers
Indicate the incidence of CA in Italy	23.0%
Indicate the first cause of CA	98.0%
Indicate the frequency of chest compressions	69.2%
Indicate the ratio between compressions and ventilations	78.8%
Performing a mouth-to-mouth ventilation in case of lack of PPE...	67.3%
How deep should chest compressions be?	88.5%
To perform insufflations into an adult patient the head must be:	65.4%
How long should you wait before using an AED device?	73.0%

Discussion

The newly licensed physicians may come across the management of a CA in various settings, for example as a doctor at sporting events, or during a shift in the clinic or in the ward. For this reason, Universities must manage outgoing guidance by providing specific practical modules. Our study aims to investigate how relevant BLS-D training is to ensure greater self report safety of the NLPs in managing a CA. From our analysis it emerges that the theoretical knowledge of medical students is not sufficient for 42.3%, but above all the theoretical knowledge does not influence the predisposition to manage a CA. This information, probably linked to the importance of the practice already highlighted in previous studies, shows how a practical BLS-D course is central to guaranteeing greater student safety. The aspects that significantly influence the safety in the management of a CA consist in having attended

an eight-hour BLS-D course or having witnessed a CA. These two aspects are important in this process. The most relevant data is the role of practical training, which has an OR of 32.9. Unfortunately, we register a large 95% CI, 5.6-193.8, but a strong significance ($p<0.01$); this could be related to the small sample and, in this sense, the same study could be re-proposed with a larger sample. However, we point out that such a large value strengthens the training project proposed by SIMED and highlights the importance of this education. It is very important to notice that 15.4% of the students attended a BLS-D course and then faced a CA, highlighting how the CA is a very common occurrence, and it represents a real challenge for the healthcare staff. As a matter of fact, training according to guidelines has proved to be essential to educate healthcare professionals to manage this kind of emergency, and to guarantee the ROSC (return of spontaneous circulation) for patients. A very significant data is the greater self confidence in managing a CA for subjects trained with a BLS-D course; this information shows how practical training is essential to be able to guarantee medical students greater confidence in managing an emergency such as the CA, in which the patient could die in a very short time. Practical training is, therefore, determinant for the operator self report safety in managing a CA. Finally, we point out that gender does not influence the predisposition to manage a possible CA.

The topic under study is essential to guarantee patient and doctor safety, for this reason training projects aimed at analyzing the object of study are necessary.

Practical experiences, training courses, and simulation of clinical scenarios should complement the theoretical training. However, it is not entirely clear what may be other practical-clinical training tools and methods in addition to attending an eight-hour BLS-D course according to guidelines, or witnessing a CA.

Conclusions

The BLS-D training course has proven to be central in the training curriculum of newly licensed physicians, in order to guarantee them a good degree of perceived autonomy in the management of the CA. Specific training projects will have to be promoted within the Medicine departments, also in light of the high number of interviewees who have declared that they have witnessed a CA.

Conflicts of interest

The authors declare no conflict of interest.

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BRIEF ARTICLE

Telemedicine and training: what could we improve?

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Abstract

Operator safety and reducing the spread of any highly contagious infectious disease represent a challenge for the future and telemedicine has shown great support in this process, but the lack of knowledge should stimulate discussion and research on this important topic. The present document is a commentary develop in the simed group traning site, a group of simulated traning who highlighted the lack of evidence about training projects aimed at building a common knowledge on telemedicine.

Brief Article

In the last years, there's been an increase in the use of territorial Emergency Systems (EMS) and Emergency Departments (EDs) by citizens [1,2]. This phenomenon is due to several factors, such as frequent users [3] and an aging population [3,4]. In addition, the management of noncritical patients by EMS systems, related to non-urgent territorial clinical needs, is increasing [2].
This phenomenon has been compounded by the pandemic caused by Covid 19, which has exacerbated the issues, greatly impacting EDs [5] and EMS [6,8], especially changing time-dependent disease networks [6].
Due to the subversion of the EU system, telemedicine models have been implemented in ERs [9], aimed at ensuring the safety of operators [9] and

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ensuring a reduction in the use of PPE [10-12]. These two aspects are very relevant, especially in reducing the spread of infectious diseases, which is catalyzed by departments such as the ED or through 118. Operator safety and reducing the spread of any highly contagious infectious disease remains a challenge for the future and telemedicine has shown great support in this process [13,14]. In addition, telemedicine tools have been shown to be safe for patients [15] even though there has been an increased use of clinial examinations [15]. This phenomenon may be due to the lack of unambiguous standards and guidelines on telemedicine [13], so more work needs to be done in future years.

Telemedicine has spread rapidly. Academia and experts agree on the future usefulness of telemedicine [16,17]. This view is also shared with patients, who have shown satisfaction [18].

The best utility of the EU system seems to be related to time-dependent diseases; in fact, it is of excellent support in the network between hub and spoke hospitals and as a support tool between specialists [16,19]. Indeed, telemedicine has been shown to be effective in time-dependent disease networks reducing the time needed to centralize or start procedures in Stroke and STEMI patients [20-22]. In addition, it has ensured an improvement in the appropriateness of secondary transports to hub facilities [23]. Despite this, the use of telemedicine in several settings has been shown to be irrelevant, such as in the follow-up of post-surgical patients [18]. In some studies, the difficulty of physicians and patients to use the devices [12] led physicians, especially from rural areas, to prefer the regular visit [12,16]. This evidence supports the importance of experimentation in new fields.

The lack of clearness about the clinical benefit and of usefulness of telemedicine in different fields could expose the patient to risks, which must be carefully evaluated. Above all, the lack of knowledge should stimulate discussion and research on this important topic with the aim of developing shared guidelines [13,24].

In fact, the term telemedicine remains very broad and generic and behind it are hidden technologies and organizational models undergoing experimentation, which is why there are so many processes under development, whose true usefulness is still doubtful and underdiscussion [25]. In addition, the studies currently present are focused on clinical elements [26], which are still useful and necessary to define patient safety, but do not help to define organizational systems [27], an essential element to ensure the process of integration with the NHS desired by all the stakeholders of the system [27].

For this reason, SIMED, an Italian society of scientific disclosure, hopes for a rapid implementation of further studies and divulgation and, above all, the development of training projects aimed at building a common knowledge on telemedicine and that can be built with clear definitions for all stakeholders, from clinicians to medical directors.

Conclusion

Training is a necessary tool to help healthcare professionals for use new technologies. Nowadays, telemedicine is spreading rapidly, but there aren't specific courses, standards traning and clear guidelines. Therefore, all training stakeholders must quickly build specific courses and training courses to ensure high standards and shared skills. This process will have to happen quickly because the spread of technologies is much faster than the development of training courses.

Conflict of Interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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