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D3.2 Medical application of ionising radiation and radiation protection in neurovascular diseases

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Abbreviations

CNS: central nervous system

IA: intracranial aneurysm

AVM: arteriovenous malformation

DSA: digital subtraction angiography

HIS: hyperacute ischemic stroke

MRI: magnetic resonance imaging; MRA: computed angiography

CT: computed tomography; CTA: computed angiography

NVD: Neurovascular disease

PCCT: photon counting CT

MAR: metal artefact reduction

API: Angiographic parametric imaging

ARE: Adverse radiation effect

INR: interventional neuroradiology

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I. Introduction

In the past three decades the treatment of vascular diseases of the central nervous system (CNS) has undergone substantial evolution. Especially the last two decades resulted in exponential evolution in the therapeutic arsenal of Neurosurgery, Interventional Neuroradiology and Radiosurgery, taking into account the advances in research and development of equipment and material, as well as the better pathophysiological understanding of neurovascular diseases, obtaining remarkable clinical outcomes.

X-ray guided endovascular interventions, performed in state-of-the-art bi-plane angiosuites, have emerged as a paradigm shift in the last 20 years for intracranial vascular diseases. They have progressively gained the status of gold standard for the treatment of many neurovascular diseases, as being minimally invasive techniques, with an important impact in the, often devastating, natural history of ischemic and malformative vascular pathologies of the CNS[1, 2].

Recent guidelines regarding the management of intracranial aneurysms and subarachnoid haemorrhage[3], as well as the endovascular therapy of acute ischemic stroke[4] designate endovascular interventions as key therapeutic modalities in the management of these diseases. Brain arterio-venous malformations, even those considered untreatable until recently, as being deeply seated or/and with deep venous drainage, may now profit from novel techniques and new endovascular materials, allowing for eradication of malformative nidi, which were unattainable 15 years ago.

Nevertheless, partly due to the relatively recent and very quickly evolving endovascular discipline of Interventional Neuroradiology, as well as due to the variability of resources in Europe, regarding these technologically advanced techniques, several gaps exist in the standardization and availability of these treatments. In addition, the exponential evolution of several technological advances and translational research breakthroughs require guiding and consensus regarding the needs and opportunities for a better exploitation of these groundbreaking resources, for the best benefit of the patient.

The EURAMED rocc-n-roll project yields a strategic research agenda in the field of medical applications of ionising radiation and related radiation protection, through a thorough analysis of research and radiation protection needs in neuroendovascular interventions, using ionising radiation. The task group 3.2 is responsible to analyse the needs of research in radiation application and corresponding protection in neurovascular diseases by identifying gaps and possibilities.

II. Literature review

Endovascular procedures for vascular diseases of the CNS employ x-ray radiation in suitable angiosuites, in order to perform very precise image-guided, endovascular interventions, without the need of an open craniotomy. Due to the nature of small-diameter and very fragile vessels, which need particular care during navigation and manipulation, with clear visibility of these fine structures, the technological advances of these angiosuites are exponential in the last two decades, Nevertheless, the research on radiation doses is a little more recent, as compared to peripheral or cardiac interventions.

In 2011, the International Commission on Radiologic Protection established an absorbed-dose threshold to the brain of 0.5 Gy as likely to produce cerebrovascular disease. Since then, studies have supported this threshold. In a study of 2014 for cerebral embolizations, brain doses resulted in a maximum value of 1.7 Gy, with an average value of 500 mGy. Median and third quartile resulted in 400 and 856 mGy, respectively. For cerebral angiography, the average dose in the brain was 100 mGy. They concluded that these

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interventions may yield high doses and recommended optimization of the imaging protocols, in order to follow the ALARA principles.[5]

In 2021, there was a multicenter effort to monitor radiation doses during diagnostic and therapeutic neurointerventional procedures; the group established reference levels for the major types of neurointerventional acts. The proposed reference levels were as follows: Proposed 3rd quartile DAP (Gy.cm2) values were 101.6 for diagnostic cerebral angiography, 199.9 for aneurysm coiling, 225.1 for stroke thrombolysis, and 412.3 for AVM embolization. According to their analysis, statistical outcomes showed male sex and presence of procedural complications were significant factors in aneurysmal coiling. Male, number of passages, and procedural combined technique were significant factors in stroke thrombolysis. In AVM embolization, a significantly higher radiation dose was found in the definitive endovascular cure group.[6]

In a very recent study aiming to measure the peak skin dose (PSD) and bilateral lens doses using radiophotoluminescence glass dosimeters during the novel technique of flow diversion for intracranial aneurysms, the authors found cumulative doses, PSD and right and left lens doses of 3818.1 ± 1604.6, 1880.0 ± 723.0, 124.8 ± 49.2 and 180.7 ± 124.8 mGy, respectively. Using multivariate analysis, the group found that body mass index and deployment time of the stent were found to be the independent predictors of PSD exceeding 2 Gy. They proposed measures such as collimation of the radiation field and optimization of radiation dose in order to reduce the radiation to the patient. [7]

To this end, there has been substantial evolution of hardware and software in angiosuites in the last 8 years; newer innovations in angiosuite software and hardware allow dose reductions of 50-70% (see chapter about software and hardware evolution). Recently, studies have shown that ultra-low dose imaging protocols during thrombectomy resulted in significant dose reduction to practitioners, angiosuite personnel and patients.[8] [9, 10] Similarly, new implantable devices with improved visibility under fluoroscopy have emerged, allowing for better visualization, without the need for high-dose protocols.[11]

III. Methodology

Task 3.2 analysed the needs of research in radiation application and corresponding protection in neurovascular pathology relevant clinical scenarios, by identifying gaps and possibilities. A panel for this task was set up by M6 which includes experts from the identified scenarios to ensure that the relevant medical and scientific communities are involved in the definition of the research needs and related priorities.

Several meetings were held both within the task and at WP-level at two WP3 workshops. In particular, 3 online meetings took place with the Task 3.2 partners to define the clinical subspecialties and imaging modalities needed between M3 and M5. In M6, an anonymous open web-based survey was prepared on WP level and distributed among the Task 3.2 panel members. The WP3 workshop on 17 June 2021 allowed for further discussion and input regarding the gaps and possibilities related to the clinical scenarios. These were analysed in order to find a consensus on the relevant clinical questions related to medical applications of ionizing radiation. A shortlist of relevant clinical scenarios with related gaps and possibilities was included in a draft document circulated among Task 3.2 members and a final consensus was obtained (M7-M8). The selection of clinical scenarios and related knowledge gaps and research needs were further discussed at the EURAMED rocc-n-roll consortium meeting in September 2021 and a refined selection presented to and discussed with relevant stakeholder groups during the WP3 workshop at the ERPW in November 2021. The relevant input was integrated in the consensus draft of Task 3.2 to be submitted to WP6

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for integration in the EURAMED rocc-n-roll SRA and roadmap. Literature research on typical exposures was performed and the state of the art in radiation protection analysed in regard to both the technical and procedural aspects.

Through online meetings and digital exchanges the group defined the potential subspecialties of the task: Interventional Neuroradiology, Diagnostic Neuroradiology, Neurosurgery and Radiosurgery-G knife were the ones retained in the initial stages. Subsequently the broad areas of clinical interest were identified: Neurovascular emergencies and elective cases Neuro-oncology Neuro-otology, vascular Neurosurgery intracranial and of the spinal cord. A consensus was reached regarding the clinical scenarios to investigate:

- Hyper-acute ischemic stroke
- Intracranial aneurysms
- Arterio-venous malformations of the central nervous system
- Carotid artery artheromatosis
- Arteriovenous fistulas and shunts
- Intracranial and cervical arterial dissections

Reaching consensus, the group decided to focus on the relevant clinical scenarios and their respective imaging and therapeutic modalities.

The group decided to focus on Neurovascular pathologies and not in inflammatory or degenerative pathologies, since the latter are explored mainly by MRI and do not profit from X-ray involved treatments, such as endovascular interventions. The imaging and therapeutic modalities implemented in these scenarios were neuro-endovascular treatments: Angio-suite (bi-plane) and computed tomography angiographies in some neurovascular pathologies.

IV. Results & outcomes

In this section under IVa, we will briefly present the state of the art, the challenges and needs related to the relevant clinical scenarios, which were identified and retained. In section IVb, we will analyse significant research advances in the fields related to the relevant clinical scenarios, including some breakthrough advances and potential game changers. These parts refer to all the clinical scenarios, since they represent advances in neuro-endovascular imaging and therapeutics and thus apply to all clinical scenarios. Research developments which concern only one relevant clinical scenario will be discussed in the IVa and not in the IVb part.

The group chose to fusion the relevant clinical scenarios “hyperacute ischemic stroke”, “carotid artery atheromatosis” and “cervical and intracranial dissections”, since the latter two represent pathologic entities leading to stroke and thus are part of the etiologic factors of ischemic stroke, which will be addressed in a common chapter.

IVa. Relevant clinical scenarios and pathologies: challenges, opportunities, needs

Intracranial aneurysms

Intracranial aneurysms represent pathologic entities which may remain silent for undetermined amounts of time, before clinical expression, which is most often rupture and intracranial haemorrhage. Intracranial aneurysm rupture results in a devastating percentage of mortality, of about 25%, which climbs up to 65%, if the ruptured aneurysm is left untreated

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within the first few days since rupture. More than half of the surviving patients suffer long term handicap. Endovascular treatment is recommended in the acute stage, in order to avoid re-bleeding.[12]

Regarding non ruptured, elective cases, the decision of treatment versus active follow up at present relies in the clinical history and co-morbidities of the patient (vascular and cardiovascular risk factors, family history of IAs, multiple IAs), as well as the size, location and contours of the aneurysm. Nevertheless, in the dawn of new data regarding the pathogenesis, growth, stability or rupture of the aneurysm's wall, these qualitative and empirical data seem to be rather general and lack precision in predicting the individual risk of rupture of an intracranial aneurysm. Moreover, the type of adapted procedure relies in the relationship of the aneurysm with the surrounding intracranial arteries, its shape and location, as well as its size and relationship to the parent artery.

The endovascular procedures are performed under x-ray fluoroscopy, in dedicated, ideally bi-plane angiosuites equipped with flat panel detectors. They are equipped with features and software such as 3D rotational angiography, which allow a precision in the range of a millimeter in the measurements of the aneurysm and its surrounding arteries, in order to correctly choose the implantable and non-implantable material during the interventions. Each intervention lasts at least an hour and since precision and safe navigation are key elements, x-ray burden is to be considered. Please refer to the section "angiosuite hardware and software innovation" to see recent advances in the angiosuite which allow optimization of the radiation dose and e.g.the reduction of metallic artefacts.

During the last 20 years, there has been an exponential evolution in endovascular techniques for the treatment of IAs and we have a wide therapeutic arsenal today, capable of addressing all locations and types of aneurysms. The techniques vary, with implantable material that address the aneurysm's sac (coils, endosaccular flow disruptors), others which are deployed in the parent vessel in order to aid with the stabilisation of the coils in the sac (self-expandable stents) and flow diverting stents, which are deployed in the parent artery, aiming to disrupt inflow of blood in the aneurysm's sac, in order for the latter to undergo thrombosis and to allow for endothelialisation of the parent vessel, over the stent's struts.[13] Devices destined to the parent artery are mainly constructed from metallic aliases such as cobalt-chromium and nitinol (nickel-titanium), with platinum parts, to enhance visualisation under fluoroscopy. They are used under dual anti-platelet therapy, in order to avoid ischemic complications. Lately new surface modification techniques have been developed, in order to provide less thrombogenicity and allow single-anti platelet treatment during implantation. These are still under investigation, with promising results.[14-16]

IAs are heterogeneous pathologic entities, comprising of seemingly sporadic cases, as well as multiple aneurysms and cases with family history of IAs, revealing a genetic component in the expression of these IAs. To date, a multitude of recent scientific data exist, from whole genomic analyses of patients harbouring multiple or bifurcation aneurysms, to flow studies, aiming to elucidate the role of genetics and environment in the pathogenesis, evolution and rupture of IAs. Flow analyses, both in vitro and in silico, studying blood flow and its parameters (shear stress, vortexes, blood inflow in the aneurysm, blood pressure etc) have allowed for more insight in the implementation of flow diverting devices as a means to treat IAs and contributed in technique and material adaptations.[17, 18] Multiple genes have already been identified[19]; as for the hemodynamic parameters' role, which are by now well studied.[20] The role of endothelial and smooth muscle cells are equally under investigation and will probably give new insight to the complex pathophysiologic mechanisms of IA growth and rupture.

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Moreover, there has been interest in the anti-aggregation profile of patients, as a factor predicting favourable or not angiographic and clinical outcome after endovascular treatment. The role of endothelial cells and their function in the healing after placement of a flow diverting stent is also interesting.[21] The roles of inflammation, metalloproteinases and VSMC have been studied, as means to predict stability or not of aneurysm's wall.[22-24] New methods for e.g. imaging of inflammation within the region of interest might provide helpful insights using ionizing radiation. However, such methodologies and approaches need still to be developed and could comprise high-resolution nuclear medicine approaches of X-ray fluorescence approaches. All these data, coming from various fields of science, need to be further analyzed in combined manners, in order to be able to obtain the means to a patient-specific, personalised decision-making, based on patient-specific angiographic, hemodynamic and biological data, for this very heterogeneous pathologic entity. The presence of omics and artificial intelligence will probably allow for a better and more global exploitation of the various advances in clinical and preclinical research.

Challenges:

- Personalised estimation of risk of rupture for unruptured IAs: need for consensus and standardization, followed by clinical evaluation and application of the newer techniques of flow dynamics evaluation including computational fluid dynamics studies, new (especially molecular) imaging approaches, radiomics studies, genetic analyses and endothelial function and response to shear stress and inflammation.
- Need for new surrogates for evaluation of the risk or rupture
- Tailoring of intervention according to anatomy, physiology of the patient: personalised medicine
- Follow up: long and tedious follow ups today, need for personalised indications and alternative techniques and treatments more stable therapeutic outcomes (etiologic ones, since for the moment we address the symptom that is the aneurysm's sac and not the cause)
- Time and exposure heavy interventions, often follow-ups needed: image and protocol optimization, alternative techniques such as CTA and MRA are recently being employed for follow-up (new techniques with better spatial resolution and optimisation of metallic artefacts or artefacts of flow -for MRI- are needed)
- better performance of endovascular devices, regarding navigation, visibility of detachable stents, anti-aggregation regimens
- Genetic burden identified for a large part but not yet exploited: need for etiologic treatments, paradigm shift
- Inequalities between countries in the availabilities of resources and techniques
- Need for more standardised consensus on management and FU, treatment of complications such as vasospasm for already ruptured IAs

Opportunities:

- **Elucidate and associate the synergies and role of the genetic, hemodynamic and biological factors for the pathogenesis and evolution of IAs**

- **Patient-specific treatment planning** with realistic CFD simulations and optimization of flow diversion techniques and materials for IA treatment

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- **New molecular imaging techniques** for risk evaluation e.g like high spatial and temporal resolution nuclear medical imaging techniques and X-ray fluorescence imaging techniques for e.g. inflammation characterisation and wall structure evaluation**.**

- **Artificial intelligence techniques**, with rapid analyses of big volume data showed promising in the automated detection of IAs from DSA and MRA studies, with very promising results. Their validity in registration of images and classification is already accepted. Furthermore, such techniques were able to combine personalised patient data and or quantification of flow techniques, in order to implement computational fluid dynamics analyses in the equations. Potential imaging-based AI applications mainly contain 6 aspects: quantification, notification tools, diagnostics, registration of images, image classification, and risk prediction for therapy[25]

- Radiomics in the management of IAs may provide additional input for the personalised estimation of **aneurysms' rupture risk**, provided that the input is valid and adequate. Radiomics features and deep learning features may be extracted from 3DRA or DSA images and the proposed new imaging methodologies and combined with the patient's clinical data in multidimensional feature fusion sets [26]
- Radiomics may also be used for the prediction of **complications and/or outcomes** of endovascular treatments. Using angiographic parametric imaging-derived radiomics features to predict complications and embolization outcomes of intracranial aneurysms treated by pipeline embolization devices[27]
- Proteomics recent studies suggest that quantitative proteomics may further elucidate the different expression of proteins between ruptured and unruptured IAs, probably in the future being able to identify proteomic profiles at risk of rupture[28]

- **Alternative-new therapeutic techniques/material**
- New, self-expandable, bioabsorbable flow diverters[29], new metallic aliases and fabrication techniques to provide better visualisation of stents[30], as well as new surface modification coatings[31] (need of single anti-platelet treatment, faster endothelial coverage)
- Patient-specific tailored devices and patient anatomy-specific tailoring of interventions
- Genetic treatments, pharmacologic or DNA modifying treatments
- -"Rehearsal" of the procedure beforehand, with the aid of 3D printed realistic flow models or in silico CFD simulations, for better patient-specific choice of material and use, as well as training, optimization of efficiency and reduction of potential complications

Arterio-venous malformations of the central nervous system and arteriovenous shunts

Brain arteriovenous malformations are congenital malformations, with a prevalence of approximately 0.05%. These lesions affect microvessels and lack a capillary bed, resulting in pathological direct shunts from arterioles to venules. Feeding arteries continue in an undifferentiated arteriovenous tangle, called the nidus, which resolves in a single or multiple, draining veins. In the nidus, the vessels are enlarged, undifferentiated and susceptible to rupture. Arterial and venous circulation are mixed within these lesions, therefore blood passes in undifferentiated vessels and in the venous part, with a high pressure, increasing bleeding risk due to vessel rupture.[32] Apart from intracranial hemorrhage, brain AVMs may

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present with seizures, headaches or focal neurologic deficits. AVMs account for approximately 1.4-2% of all strokes and 9% in all primary intracranial haemorrhages; around 50% of the patients harbouring an AVM present with an ICH. Due to the heterogeneity of AVMs, annual hemorrhagic risk may be as low as 0.9% per year for unruptured AVMs with superficial drainage, or as high as 34% per year for ruptured AVMs that are deeply seated, have associated aneurysms, and have deep venous drainage.[33]

For acutely ruptured lesions, the treatment of choice is the obliteration of the site of rupture by targeted endovascular embolization, treatment for hydrocephalus and other complications, if present, and target the eradication of the nidus in the weeks or months following rupture in order to avoid rebleeding. The latter can be done by surgical or endovascular means, or by a combination of both, depending on the location, angio-architecture, and size of the malformation. Gamma-knife radiosurgery may be employed for small remnants, with good angiographic outcomes, even though a latency period of around 24-36 months is usual, until the nidus is eradicated; during this period the risk of re-rupture is not eliminated.

Unruptured lesions may be actively followed or treated with one or combination of surgical, endovascular and g-knife radiosurgical means. The choice of technique depends on the size, location and angio-architecture of the lesions. The Spetzler-Martin score[34] is widely used to assess the severity of the lesion, as a tool for therapeutic decision making. It employs the nidus size and location, as well as the venous drainage patterns, in order to categorise brain AVMs in I-V categories, with increasing risk of rupture and challenges as to treatment.

Endovascular embolization treatments, with liquid embolic materials under constant fluoroscopic guidance in angiosuites, have been employed since around 30 years; initially NBCA was used as an embolic agent, in order to reduce the nidus size and the high flow components of the bAVM, often followed by surgical resection. With the initiation of the non-surface modifying embolic agents, such as the NBCA and the evolution of microcatheters and dual-lumen balloons, there has been an ever-evolving paradigm shift in the treatment of brain AVMs, with the possibility to cure otherwise unattainable, deeply seated or with deep venous drainage lesions (Spetzler-Martin III to V), in one or two embolization sessions.[35-38]

As opposed to adjunctive or emergency endovascular embolization for bAVMs, endovascular nidus obliteration techniques are novel approaches in the therapeutic arsenal, made possible due to the advances both of the interventional material and of the imaging methods in the angiosuite. [35-38] It is well understood by now that the goal of any treatment for brain AVMs should be the total obliteration or eradication of the nidus, since any partial treatment strategy, if failed to follow through until total nidus exclusion, will increase the hemorrhagic risk of rupture of the brain AVM, as compared to its natural history. In the previous decades, due to lack of appropriate techniques and gaps in the knowledge of the pathogenesis mechanisms of the AVMs, partial treatment of nidi was performed. To date, this is no longer acceptable, with the knowledge we gained of these pathologic entities; there are several mono- or multi- modality strategies which allow for nidus eradication, in one to two therapeutic sessions. Angio-architecture, location and hemodynamic parameters should undergo thorough examination by highly specialised practitioners, in order to propose the appropriate treatment strategy.

Angio-architecture may be extremely complex in brain AVMs, with multiple feeding arteries, which are not always visible in MRA or DSA studies, partially due to arterial steal. Venous outlets may be equally complex to analyse or visualise, due to the overlapping of voluminous nidi, vascular steal, or small size. These structures, as well as the whole hemodynamic presentation of the lesion and its relationships to the surrounding structures, are very important for the appropriate treatment planning and the good clinical outcome. At present,

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fusion MRI-3DRA imaging techniques are employed to better differentiate the avms' components; new segmentation algorithms are proposed to differentiate nidus from veins; hybrid navigation techniques have also been proposed, with MRI fusion. Spatial resolution and the close vicinity of these structures, remain issues for optimal visualization. Techniques of quantification of flow employed in the angiosuite may prove very useful tools in the near future.

Pathogenesis and evolution of brain AVMs is multifactorial, comprising genetic, hereditary, and epigenetic parameters, which interact in complex pathways, which are not yet completely elucidated. The new era of "omics" has allowed large-scale examinations of contributory genetic variations in human sporadic bAVMs. New findings regarding the pathogenesis of bAVMs point out to changes in endothelial and mural cells, that result in increased angiogenesis, pro-inflammatory recruitment, and breakdown of vascular barrier properties, that may result in haemorrhage; a greater diversity of cell populations that compose the bAVM microenvironment may also be implicated and complicate traditional models. Genomic sequencing of human bAVMs has uncovered inherited, novel and somatic activating mutations, such as KRAS, which contribute to the pathogenesis of bAVMs. The emerging genomic and transcriptomic findings underlying pathologic cell transformations in bAVMs derived from human tissues seem very interesting; the application of multiple sequencing modalities to bAVM tissues is a natural next step for research.[39]

Arteriovenous shunts of the central nervous systems (dural arteriovenous fistulas, pial shunts)

Arteriovenous shunts represent complex pathologic entities, where there is direct communication between arterial branches and venous sinuses or intracranial veins, without the interference of a capillary bed. As opposed to the bAVMs, there is absence of nidus; these are direct artery-to-vein shunts. They show a risk of venous rupture, due to high flow situations; the latter increases with the presence of some angioarchitectural characteristics, such as draining in a cortical vein or cortical vein reflux, especially with venous dilatations. Arteriovenous shunts of the CNS are classified by several grading scales (Barrow's, Cognard-Merlan[40]), in order to assess the individual risk of rupture. Their etiology may be traumatic or non-traumatic. The latter may be due to various factors involving inflammatory processes, such as previous thrombosis and recanalization. Pial AV shunts show more often a genetic component in their pathogenesis and a high risk of intracranial rupture. Their treatment is currently mostly endovascular but may also be surgical or radiosurgical (gamma-knife), depending on location.

The therapeutic principles and techniques are similar as those for brain AVMs. The goal of treatment is to occlude completely/eradicate the shunt zone, in order to avoid rupture. The advances in the liquid embolic material, in microcatheters and micro-balloons and in the techniques used for brain AVMs have also reinforced the therapeutic arsenal of these arteriovenous shunts. The challenges regarding angioarchitecture and analysis of anatomy and flow are similar as those of brain AVMs, thus they benefit from the same advances in research and development as those.

Challenges:

- Currently lack of consensus for treatment for unruptured cases, need for guidelines

- Inhomogeneity of bibliographic data regarding the different endovascular techniques, historic techniques from the 90s with mediocre outcomes out shadow the new, rapidly

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evolving endovascular techniques of the last decade, which yield very promising angiographic and clinical outcomes; gap regarding optimal management consensus incorporating novel techniques

- Large, multicentre studies needed on the effectiveness of novel endovascular techniques, which show very promising results for the eradication of the nidus and excellent clinical outcomes

- Genetic print of the disease, which shows genetic polymorphism, role of epigenetic mechanisms and blood flow under investigation, same with hemodynamic influence in cellular level, regarding pathogenesis and evolution of bAVMs, results very interesting, need validation, correlation, and exploitation

- Anatomically complex pathologic entities, especially in larger AVMs difficulty in discerning arterial from venous site; hybrid DSA coupled with MRA techniques seem promising, same for latest angiosuite software evolutions

- Endovascular techniques need highly specialised and skilled practitioners, only available in dedicated tertiary centres

- Need for appropriate training; rare pathologies which until now should be treated in highly specialised centres

Opportunities:

- **Optimization of software tools to differentiate the arterial from the venous site in the nidus, partly based on AI methods**

- **Evolutions in angiosuite software and hardware, coupled with flow quantification techniques (4Dphase contrast MRA, other...) and CFD in silico studies, may allow better treatment planning with safer outcomes**

- **Better understanding of pathophysiological mechanisms of formation and evolution of bAVMs through molecular and omics techniques**

- **Improved and novel endovascular material and techniques may allow eradication of nidi in a single embolization session, without latency period**

- **Radiomics for diagnosis and rupture risk prediction**
  Angiographic parametric imaging (API)–derived radiomics features have been extracted from DSAs of patients with AVMs in order to differentiate ruptured and unruptured lesions[41]

- **Omics and Molecular Biomarkers**
  Increased inflammation in cellular level and endothelial instability are potential biomarkers for AVM assessment of rupture risk: cytokines (IL-6, IL-17A, IL-1b, and TNF-a), NOTCH pathways, MMP-9, and VEGFA were associated with an increased hemorrhage risk in patients with bAVM[42] More than six microRNAs have been reported to play a role in the evolution of BAVMs, which could be potential molecular biomarkers; more research is needed [43]

- **Emerging treatments based on molecular information**:

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Even though gene therapies for intracranial aneurysms and AVMs have been discussed for more than a decade, it is only recently that whole genome analyses have provided us with a genetic background for these diseases. Their genetic polymorphism is still being investigated, while the role of shear stress and hemodynamic environmental triggers are also under investigation, with interesting initial insights.

Genotype-targeted molecular inhibition could be a potential emerging treatment for bAVMs[44]. Corresponding imaging methodologies would be helpful.

- **Endovascular or liquid biopsy** refers to the concept under development of obtaining molecular signature through blood components, without necessity of a biopsy, allowing for a minimally invasive potential diagnostic tool [45, 46]

Hyper-acute ischemic stroke, cervical and intracranial atherosclerosis, and dissections

Brain ischemic stroke is the leading cause of disability and the 2nd most often cause of mortality worldwide. According to the World Stroke Organization, over 13.7 million stroke attacks are reported each year, of those cases 60% are under the age of 70, making it a major societal problem worldwide.[47]

The mechanism of hyper-acute ischemic stroke concerns a thrombus (clot), which acutely obstructs an intracranial or cervical artery, depriving the brain parenchyma downstream from oxygen and nutrients and thus provoking cellular death (necrosis). When this occurs, it is of utmost importance to remove the obstacle as soon as possible, since during every minute of obstruction 1.400.000 neuronal cells undergo necrosis, in other words non reversible cellular death. During the last 20 years, endovascular techniques and pharmacological approaches have been developed, in order to timely remove the thrombus and free the cerebral vasculature from the etiologic factor of the ischemic stroke. Intravenous thrombolytic drugs (pro-urokinase, urokinase, recombinant tissue plasminogen activator or alteplase, tenecteplase…) have been employed within the first 4.5 hours since symptom onset, with very good results for distal intracranial branches. For large vessel occlusions endovascular means, initially intra-arterial thrombolysis and since 2008 mechanical thrombectomy, when possible assisted by transvenous thrombolytic treatments, seem to be very efficient, within the first 6-12 hours after symptom onset.[48-51]

In the last 8 years, there has been a worldwide revolution in the recommendations for the management of the hyperacute ischemic stroke, with the mechanical thrombectomy becoming the game changer of patients' clinical outcome, preventing catastrophic clinical outcomes and allowing for patients to recover from stroke without handicap, when performed timely.[52-54] Currently, a multitude of devices and techniques of thrombectomy exist (large-bore catheter thromboaspiration, stent-retrievers and similar devices, combined techniques, micro-stents for distal locations, variable-diameter stent retrievers….), allowing to access and successfully perform thrombectomy in patients of all ages and anatomic configurations. There is actually no cut-off of age for this intervention, which can be performed under general anaesthesia or neuroleptanaesthesia.

The indications for mechanical thrombectomy have also been expanding, from a time window of 6 hours since onset of symptoms for endovascular approaches in the past, to imaging-based decision making outside of the original time window, according to the presence or absence of "penumbra", which represents potentially salvageable brain tissue. Brain MRI, with diffusion-perfusion studies, is the gold standard as the decision making tool,

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allowing for wake-up strokes and strokes of undetermined time of onset to be considered for thrombectomy. CT-CTA-CT perfusion studies can also be performed effectively for the triage of patients eligible for thrombectomy.[55-57] The available imaging modalities for the decision-making process in hyperacute ischemic stroke vary from country to country and from region to region. In France, there is 24/7 coverage of neurovascular emergencies by MRI; in many other countries only CT is available, especially during the night hours. In order for thrombectomy and IV thrombolysis to be efficient, time and diagnostic evaluation are both of utmost importance.

Etiology of stroke

Large-vessel hyperacute ischemic stroke is largely divided in two categories: embolic (or cardioembolic) stroke, where the thrombus or clot has travelled with the blood flow until the site of occlusion and thrombotic stroke, where the thrombus and occlusion is produced in the artery locally. Atrial fibrillation and cardiac causes, or hypercoagulative states account for most embolic strokes; local atheromatosis or dissection are the reasons for non-embolic or thrombotic stroke. **Carotid artery atheromatosis** or **cervical artery dissections** may result in tandem occlusions, with stenoses at the carotid artery and embolic complications intracranially, from a thrombus which was created at the site of the lesion and then detached and embolised in intracranial arteries, usually at the Willis level. In these cases, the intracranial occlusion is addressed primarily by mechanical thrombectomy and then the lesion in the carotid or other cervical artery is addressed, either pharmacologically (statines, anti-platelet therapy for atheromatosis or anticoagulant treatment for dissections), either with emergency angioplasty and stenting, in cases where important arterial lumen stenosis or occlusion produce hemodynamic stroke. MRI investigations, with perfusion studies, are crucial in these cases, in order to evaluate the impact to the brain perfusion of these tandem lesions and timely adjust the therapeutic strategy.

Regarding predisposing factors for ischemic stroke in general, these include cardiovascular risk factors such as, arterial hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, alcohol consumption, obesity, and lack of physical movement, as well as hypercoagulable states (prothrombotic states or thrombophilia). Monitoring and regulating these states with appropriate treatments is mandatory, in order to decrease the incidence of ischemic stroke.

Challenges:

- improve times from symptom onset to hospital and to needle (in-hospital times), in order to improve outcomes of thrombectomy (awareness of population in order to call the emergencies early, transfer of patients, mobile units, etc)

- define imaging profiles for optimal clinical outcomes or prevision of procedural complications of thrombectomy

- define clot types and anatomical types favourable for specific techniques of thrombectomy

- prevention of stroke, definition of patients at risk

- new and improved devices for distal intracranial locations

Opportunities and recent evolutions:

- **Radiation dose reduction and image optimization**

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Since ischemic stroke represents the second cause of mortality and the first cause of handicap worldwide, the issue of radiation exposure and fluoroscopy time in mechanical thrombectomy became very interesting. Retrospective data have showed that the interventionalists' experience played an important on procedure time, fluoroscopy time, and radiation exposure during interventions[58]: A very recent study of 2022 concludes that occlusion type, number of recanalization passages and dose program determine radiation dose in endovascular stroke thrombectomy.[59] Recent advances in the angiosuite hardware and software are discussed in the next chapter.

- **Portable diagnostic devices**

Since CT and MRI are not available in every healthcare facility, alternative, portable and more economical solutions are currently under investigation and development. These research and development efforts often employ alternative imaging methods for the detection of hyperacute stroke. Among these are volumetric impedance phase-shift spectroscopy, microwave tomography, infrared imaging and Doppler ultrasound.[60] Even though they lack spatial resolution and sensitivity, some of them may soon prove very useful for the management of patients in rural areas or in cases where the triage for transport in the tertiary centre is needed, but there is no available CT or MRI on site. Other options could be potentially developed and would help for better and faster treatments of stroke patients with interventional procedures using ionising radiation.

- **Radiomics**

The MRI study of ischemic "penumbra", otherwise the tissue that is potentially salvageable through treatment, is traditionally derived from the qualitative deduction of the ischemic core, which is represented by the DWI positive lesions in the brain, from the area which suffers perfusion deficit, without yet evident lesions in the FLAIR sequence. Radiomics in the diagnosis of salvageable brain tissue for hyperacute ischemic stroke represents a novel research field, aiming to objectify and quantify the salvageable brain tissue, employing omics techniques in order to extract imaging signatures from large cohorts and employ them to better stratify the "penumbra".[61]

- **Blood biomarkers**

Glial fibrillary acidic protein (GFAP), is a structural astrocyte protein, which seems to be a very promising blood biomarker of acute stroke and may effectively differentiate ischemic from haemorrhagic stroke.[62] Several more proteins, such as the S100b, are under investigation with promising initial results

MicroRNAs are non-coding RNAs with a length of around 22 nucleotides that regulate gene expression by destabilizing and repression translation of complementary mRNAs. Several of them have been identified within the last 8 years, as potential biomarkers for the evolution and prognosis of ischemic stroke. Some of them have been associated with symptom severity and infarct volume and were potential markers of clinical outcome. They have been suggested also as potential biomarkers for early stroke diagnosis in the emergency setting.[60, 63]

- **Omics, Metabolomics**

Mass spectroscopy analyses with omics techniques seem to yield some promising directions for their use in the etiology and outcome of ischemic stroke. In a recent proteomics and metabolomics study of mass spectroscopic analyses of fresh thrombi collected from thrombectomies, the authors found that the combined proteomic and metabolomic signatures of cerebral thrombi had a better diagnostic performance than the classical predictors

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commonly used in clinical practice. They could also differentiate with this technique the embolic origin of the thrombus. [64]

- **miRNA-based treatments**

Resent advances in basic research point out miRNAs as potential modulators of brain ischemia, mainly by modifying inflammatory response, through their potential to pass, under certain circumstances, the BBB. They seem to have potential for novel therapeutic strategies to improve functional outcome in stroke patients in the early stages of stroke[65-68]

- **Remote/robotic interventions, augmented reality and teleproctoring for faster thrombectomy times remotely, instead of transferring the patient** (see dedicated chapter in IVb)

IVb. Breakthrough advances in research related to task 3.2 pathologies, game changers

In this chapter the task group focused on recent advances and trends that seem promising, or are breakthroughs, even potential game changers. These advances impact every relevant clinical scenario and pathologic entity described within the group's work.

Angiosuite hardware and software innovations

Digital Subtraction Angiography (DSA) remains the gold standard of diagnosis and the sole modality of endovascular treatment to date for neurovascular pathologies. Malformative diseases such as arteriovenous malformations and shunts, as well as intracranial aneurysms benefit not only from anatomic depiction, but from a detailed hemodynamic evaluation, through selective and hyperselective runs.

Computed Tomography Angiography (CTA) is reliable technique, often used in screening and follow up of lesions such as IAs and stroke, which does not provide selective, hemodynamic appreciation. Magnetic Tomography Angiography (MRA) is equally reliable technique for screening, diagnosis and follow up; it has a high predictive value for cervical and intracranial dissections. It is also used for already treated IAs, since it produces less metallic artefacts from the endovascular coils or other devices. Diffusion and perfusion MRI studies are the gold standard for early diagnosis and therapeutic decision making of hyperacute ischemic stroke.

Digital Subtraction Angiographic suites or angiosuites have undergone substantial evolution in the last decade, with bi-plane ones being the state-of-the-art hardware for neuroendovascular therapeutic procedures. They allow safe and precise navigation, choice of implantable material and safe apposition. Nevertheless, dose-reduction and dose-optimization evolutions have been deemed important in the last decade; several hardware and software improvements and novelties have emerged in the last 5 years as a result.

State-of-the-art angiosuites have currently sophisticated image post-processing chains, intended to optimise (patient) exposure and image quality. They have multiscale implementations of *real-time motion correction*, *image contrast-dependent temporal averaging*, and *image noise reduction*. Hardware optimization, including the use of *Cu beam filtration*, depending on x-ray tube loading and a narrower x-ray pulse width have allowed for around 65% of dose reduction, as compared to previous generation angiosuites.[69] Reductions in total dose-area products of 62% to 75% have been achieved in the last 5

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years, without significantly affecting fluoroscopy time, procedure duration, and the number of acquired images.[8]

Very recent advances in hardware, published in 2021,[9] include:

- more *powerful X-ray tubes*, flat-emitter technology with reduced tube focal spot sizes (0.3, 0.4 and 0.7), which are automatically adjusted, for sharper images at the same dose, better visualization for stents and small structures

- *increased maximum pulse power* of 90 kWp (better penetration of thick body parts), plus *increased copper pre-filtration* reduces patient entrance dose at same image quality level by spectral beam hardening.

- *increased tube power* to 5000 W

- *automatic Exposure Control* (AEC), resulting in shorter pulses with higher tube currents, leading to *less motion blur*, as well as more frequent use of smaller focal spots, ensuring *better image quality* and / or *lower dose*.

- Amorphous silicon detector matrix applying CsI as scintillator material, the pixel pitch is 154 µm and an image matrix of 2,640 × 1,920 pixels, scintillator layer of 750 µm which increased the X-ray detection efficiency (DQE) to 77% for typically used beam qualities.

Along with improved software components enhanced image processing algorithms, the authors reported a reduction of cumulative DAP of 72%

Spot fluoroscopy: a novel innovative approach regarding fluoroscopic images, which allows to reduce radiation dose during roadmap in neurointerventional procedures, by allowing radiation in a selected FOV of the road map image[70]: reduction of 50% of the total fluoroscopic dose-area product; the use of SF did not lead to an increase in fluoroscopy time or an increase in total fluoroscopic cumulative air kerma, regardless of collimation

Spot ROI: A novel functionality aimed at x-ray dose reduction, which can be used in fluoro and DSA , features a rectangular or square ROI of any size, which can be freely moved within the FOV at any time and as often as the operator wants; the FOV, outside the ROI, is still visible (additional Cu attenuation); total fluoroscopic DAP reduction is reported to be around 50% [10]

In 2021, in a comparative study of traditional decision making versus angiosuite decision making with the novel flat-panel detector CT assessment the authors found significant reduction of door-to-puncture, door-to-reperfusion and picture-to-puncture times. Directly transferring patients to the neuroangiography and using flat-panel detector imaging to determine eligibility for endovascular thrombectomy was feasible and safe. This approach may result in a reduction in times to treatment potentially leading to better clinical outcomes. Larger studies are needed.[71] This solution to the best of our knowledge is best suited for centres basing their decision making on CT-CTA-CT-perfusion studies; it is yet to be established whether the benefit from reduced times will counterbalance the valuable information provided by MRI-MRA-MR perfusion studies.

Digital variance angiography

Digital variance angiography (DVA) is a novel image processing method, based on kinetic imaging, which allows the visualization of motion on image sequences generated by penetrating radiations. DVA is a specific form of kinetic imaging: it requires angiographic image series, which are created by X-ray or fluoroscopic imaging and by the administration

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of contrast media during various medical procedures.[72] The resulting single DVA image visualises the path of contrast agent with relatively low background noise; it calculates the standard deviation for each pixel position in an image series. There are some very interesting outcomes of this technique: contrast media-induced changes are amplified, the background noise is suppressed, and image quality is improved, while achieving contrast media and radiation dose reduction.[73]

Photon counting

Current clinical CT systems rely on energy-integrating detectors (EID), which measure the total x-ray energy reaching the detector during the measurement period. The photon-counting detectors (PCD) in a PCCT system count the exact number of incoming x-ray photons and also measure their energy individually. As a consequence, PCDs always obtain spectral information and can effectively filter out electronic noise unlike EIDs, resulting in significantly improved signal-to-noise ratio.

In a very recent study on image quality of a spectral photon-counting detector (PCD) computed tomography (CT) system for evaluation of major arteries of the head and neck, the authors reported significantly higher image quality scores, as compared with single-energy CT detectors, with lower image noise ($P < 0.01$) and less image artefacts ($P < 0.001$). Photon-counting detector image noise was 9.1% lower than EID image noise (8.0 +/- 1.3 HU vs 8.8 +/- 1.5 HU, respectively, $P < 0.001$). Arterial segments showed artefacts on EID images due to beam hardening that were not present on PCD images. Iodine maps had 20.7% higher CNR compared with nonspectral PCD (65.2 +/- 9.0 vs 54.0 +/- 4.5, $P = 0.01$), and virtual monoenergetic image at 70 keV showed similar CNR to non-spectral images (52.6 +/- 4.2 vs 54.0 +/- 4.5, $P = 0.39$). [74]

In a study of 2022 Photon Counting CT Angiography of the Head and Neck was found to be more favourable than conventional techniques[75]. Furthermore, in neurovascular diseases treated by endovascular means, metal artifact reduction of neurovascular coils is important for the correct evaluation of the evolution of the disease and treatment. In another study of the current year, comparing photon-counting detector CT versus energy-integrating detector CT of a standard brain imaging protocol the authors found significant reduction of metallic artifacts related to coils and implantable material.[76]

Hybrid and combined imaging techniques in angiosuite

In a recent study of 2021 the authors describe a configuration of an angiosuite which co-exists with a direct access to a 3T MRI scanner, allowing the patient's bed to be moved from DSA to MRI and back. They used this hybrid configuration for the treatment of hyperacute ischemic stroke and found out that significant MRI results influenced clinical decision making in one of three ways: whether or not to perform initial or additional mechanical thrombectomy, whether or not to place an intracranial stent, and administration of antithrombotic or blood pressure medications.[77] This configuration may be useful in all endovascular neurovascular interventions.

Fusion imaging techniques

This technique combines real-time fluoroscopy with a previously performed CTA or MRA, in order to facilitate navigation in supra-aortic and cervical arteries and veins. It allows for less CM application and x-ray fluoro times and allows safe navigation through tortuous anatomies. It employs exploitation of a previous CTA or MRA study, which is fusioned, by appropriate software, with the angiosuite examination, in order to obtain a fusioned (or virtual) road map. The authors found the technique very useful for primary access (navigation of the guiding catheter or long introducer sheath), with good spatial accuracy. The technique

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was feasible and safe; it is not yet fine-tuned to become adapted to smaller intracranial arteries but seems promising.[78] Further improvements in this context could be achieved by even better registration tools e.g. based on AI methods.

Genetic modification treatments, treatments based on molecular information

These were discussed in the previous chapter for each relevant clinical scenario; these emerging techniques seem very promising, but further research is needed.

Omics, Radiomics

These were discussed in the previous chapter for each relevant clinical scenario.

Liquid biopsy

See chapter regarding bAVMs

Big data, artificial intelligence and machine learning

Potential imaging-based AI applications mainly contain 4 aspects: quantification, notification tools, diagnostics, and risk prediction for therapy.[25] These were discussed for each relevant clinical scenario separately. Registration may be seen as a new relevant application as it would foster fusioning of images as describes previously.

In this chapter we will mention a new technique, which may be applicable in all fields of interventional neuroradiology, the **artificial Intelligence-Based 3D Angiography**, which aims to provide better visualization of complex cerebrovascular pathologies.[79] As a novel post-processing method for 3D imaging of cerebral vessels, it allows to omit the use of a mask, as currently performed in 3DRA, thus allowing for considerable reduction of the patient radiation dose. In a recent study, datasets of IAs, AVMs and dural fistulas, which were reconstructed by conventional and by the prototype software, were analyzed in terms of image quality, diameters of vessel for injection, vessel geometry index and specific qualitative/quantitative parameters of AVMs (e.g. location, nidus size, feeder, associated aneurysms, drainage, Spetzler-Martin score), dAVFs (e.g. fistulous point, main feeder, diameter of the main feeder, drainage), and cerebral aneurysms (location, neck, size). The specific qualitative/quantitative assessment of 3D angiography revealed nearly complete accordance with 3D-DSA in AVMs, dAVFs and cerebral aneurysms. Assessment of the geometry of the injection vessel in 3D angiography data sets did not differ significantly from that of 3D-DSA.[79] It seems that 3D angiography is a promising post-processing method that will allow a significant reduction of the patient radiation dose.

Augmented reality and mixed reality interventions

Augmented reality (AR) technology consists of adding digital information to the direct view of an existing physical environment. With specifically designed headsets it is possible for the medical practitioner to see virtual objects superimposed on the real environment. Data from various sources can be projected and exploited during the intervention. The use of traditional screens for image navigation may be reduced or theoretically omitted.[80] Within the last 5 years several prototypes have been developed, providing potentially the possibility to perform:

- Procedure planning by leveraging data and artificial intelligence

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- Procedure guidance by using mixed reality
- Procedure optimization, using data from previous imaging studies and radiomics biomarkers
- Radiation optimization and dose reduction
- Tele-proctoring, tele-guidance-support from experts, long distance training
- Coupling with robotic technology

Robotic assisted interventions, alternative navigation paradigms and remote interventions

Robotic platforms for robotic-assisted endovascular interventions exist in peripheral and cardiac interventions since around 8-10 years. They are able to provide procedure optimization, with radiation, time, and material reduction. Since first in-human evaluation there has been reported significant (97.1%) reduction in radiation exposure to the operator performing the robotic PCI procedure.[81, 82] Nevertheless, the finesse needed in order to safely navigate the thin, tortuous and very fragile cerebral vasculature has only recently been obtained.

The first in-human robotic-assisted cerebral aneurysm treatment using a dedicated robotic system has been published in 2020. Since then, the group has been able to successfully complete a small case series of patients harbouring IAs, treated with various endovascular techniques (4 with neck-bridging techniques and two with flow diverters). All procedures were completed robotically, without need for unplanned manual intervention. The technical success rate was 100%. There was no morbidity or mortality associated with the procedures. One year follow-up imaging showed that four aneurysms were completely obliterated (Raymond-Roy Occlusion Classification (RROC) class I) and the remaining two were occluded with a residual neck (RROC class II). In the series, the average duration of the intervention was around 85 min, which is a very good performance. The robotic system demonstrated a precise control over the microcatheter, wire and stent during aneurysm treatment. The authors concluded that robotic neuro-procedures seem to be safe and effective and demonstrate stable occlusion results in the midterm follow-up. They also stated that use of robotics in medicine may enable increased technical accuracy, reduced procedural time and radiation exposure, and remote completion of procedures.[83]

In this direction, remote, robotic-assisted interventions are considered a potential game changer for interventional neuroradiology and neuroendovascular procedures, which will allow patients to profit from the same expertise as in large tertiary centers, even though in remote, rural areas. There are multiple experimental settings currently evaluating the technique, with promising results so far.[84, 85] Different approaches are implemented in the way to navigate the microcatheters and material in the cerebral vasculature, among which magnetic manipulation, which seems to be able to address challenges of distal access in very tortuous anatomies, which are often encountered in ischemic stroke.[86]

The solution of remote tele-proctoring takes advantage of connected or intelligent angiosuites and augmented reality in order for a very experienced practitioner to guide remotely a less experienced practitioner in performing a demanding intervention, such as mechanical thrombectomy for hyperacute ischemic stroke, carotid or intracranial angioplasty, embolization of an IA etc. In a recent study comprising a series of 10 cases, a neuroendovascular fellow successfully performed the interventions through cloud-based tele-proctoring platform guidance from a senior interventional neuroradiologist from a remote site.[87]

These evolutions have the potential to be game changers in the management of neuroendovascular pathologies. Regulation, ethics and consensuses will be of crucial importance in the next years, in order to be able to exploit the tremendous potential of these research advances for the best interest of the patients.

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Throughout the work of the task group, the following needs were identified for standardisation of neuroendovascular procedures throughout Europe for access to dedicated centers of neuroendovascular interventions and communication of data throughout centres:

- Availability of clinical data among centers for clinical use
- Availability of research databases for research purposes
- Consensus regarding therapeutic and FU protocols throughout Europe
- Consensus and directives regarding angiosuite standards, functionality and education of interventional neuroradiologists and paramedical personnel.

Potential game changers

The following potential game changers were identified:

- Genetic modification treatments in neurovascular diseases
- Artificial intelligence, radiomics, omics
- Robotic and remote interventions
- Augmented reality and mixed reality interventions

V. Conclusions & recommendations

Endovascular neurointerventional procedures have allowed for minimally invasive treatment for a multitude of CNS vascular pathologies, for all ages and gravities of clinical presentation. With the initiation of endovascular thrombectomy for hyper-acute ischemic stroke they become game changers for population health and society, allowing changing the natural history of one of the most devastating pathologic entities worldwide. Big data analysis will give us insights that we never had the opportunity to have before, with the possibility to exploit large numbers of images from rare diseases such as IAs and AVMs. Augmented reality, robotic interventions and remote interventions are already being evaluated for INR interventions and will probably change the landscape of the field and become game changers. New ethics, consensus and regulatory pathways will be shortly needed in order to implement these breakthrough evolutions in everyday clinical practice.

Summary list of the identified potential research topics

- Elucidate and associate the synergies and role of the genetic, hemodynamic and biological factors for the pathogenesis and evolution of intracranial malformative diseases (intracranial aneurysms, brain avms)
- Artificial intelligence-radiomics and molecular imaging techniques in the evaluation of risk of rupture of IAs
- Patient-specific treatment planning with realistic CFD simulations and optimization of flow diversion techniques and materials for IA treatment
- Patient-specific treatment planning for brain AVMs based in new software in the angiosuite, artificial intelligence techniques (artificial Intelligence-Based 3D Angiography) and omics-radiomics
- Better understanding of pathophysiological mechanisms of formation and evolution of bAVMs through molecular and omics techniques
- Improved and novel neuro-endovascular material and techniques

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- Molecular Biomarkers-liquid biopsy for brain AVMs
- Emerging treatments based on molecular information: Genotype-targeted molecular inhibition for intracranial aneurysms and AVMs
- Radiomics, Omics, Metabolomics and Blood biomarkers in the diagnosis of salvageable brain tissue for hyperacute ischemic stroke
- miRNA-based treatments for brain ischemia
- Remote/robotic interventions, augmented reality and mixed reality interventions and the associated software and hardware developments

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