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## Microspheres as Tools to Predict Animal Models for the Multi-Infarct Dementia

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**Abstract:**

Multi-infarct dementia (MID) is a severe type of vascular cognitive impairment caused by the accumulation of multiple cerebral microinfarcts (MMIs). MID, the most prevalent vascular contributions to cognitive impairment and dementia (VCID) subtype, is becoming an important health concern as life expectancy rises, particularly for those with age-related risk factors such as diabetes, hypertension, and cardiovascular disease. Several animal models have been developed to mimic the MID pathological conditions that provide useful information for the study of new drugs in MID. Microspheres are classified as medical devices rather than pharmaceuticals because they constitute a therapeutic product. Practically speaking, this means that these agents must adhere to different rules than more conventional treatments. Microsphere-induced embolism (ME) resulting in MID depends on the number of microspheres. This review provides an overview of the dementia and properties of microspheres and their predicted role in animal model development for the management of MID.

**Keywords:** Multi-infarct dementia, multiple cerebral microinfarcts, microsphere, animal model.



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## INTRODUCTION

Dementia is a significant public health challenge of the 21st century, affecting around 55 million people worldwide, and projected to nearly triple by 2050 (Livingston *et al.*, 2024). Dementia is a syndrome comprehensively including a large number of different brain disorders. It mostly defines memory disorder as the basis, but cognitive impairment is often severely damaged even when speech and executive functions are affected, and memory is relatively kept (Korczy *et al.*, 2012). Recent advances in dementia research have substantially enhanced our knowledge of several modifiable risk factors associated with dementia. Evidence has identified a range of potentially modifiable risk factors for dementia, including sensory impairments, cardiovascular risk factors, lifestyle behaviors, metabolic conditions, psychological factors, social determinants, and environmental exposures (Livingston *et al.*, 2024).

### Vascular dementia

Vascular dementia (VaD) is the second most common form of dementia in the elderly after Alzheimer's disease (AD). VaD is a progressive disease that results from reduced blood flow to the brain and affects cognitive abilities, particularly executive functioning (Venkat *et al.*, 2015). VaD may be caused by a reduction of blood flow to the brain, which may or may not be linked to a stroke. VaD includes: multi infarct dementia which is characterised by multiple small strokes, single infarct dementia which is caused by a single major stroke with damage to the hippocampus, small vessel disease (SVD) and vasculitic dementia in which patients also have migraine like headaches caused by inflammation of blood vessels (Bir *et al.*, 2021).

VaD is a complicated neurodegenerative illness that affects cognition and memory. Cognitive impairment can be caused by many mechanisms, one of them including damage to blood vessels that provides deep white matter (WM) to the brain inducing silent, multiple focal, brain microinfarcts or strokes, vascular functional disorders, and a decrease in cerebral blood flow (CBF) and induction of cerebral

parenchymal cellular damage (Laloux and Brucher, 1991; Rapp *et al.*, 2008; Steiner *et al.*, 1980). It is particularly important to actively prevent and treat VaD and to study effective drugs. Many researchers regard the design of an ideal animal model as the first step in the study of VaD treatment (Venkat *et al.*, 2015).

The risk factors of VaD are age, coronary artery disease, midlife cholesterolemia, high dietary saturated fat and cholesterol, hyperhomocysteinemia, midlife diabetes mellitus, midlife hypertension, obesity, metabolic syndrome, arteriosclerosis, smoking, and poor education (Korczy *et al.*, 2012).

### Multi-infarct dementia

Multi-infarct dementia (MID) is believed to be the most common form of VaD. It is a cumulative result of multiple strokes that do not necessarily show symptoms and happen at the same moment (Hachinski *et al.*, 1974). The symptoms of MID often consist of well-known impairment in executive functions such as attention, working memory and perceptual speed, mild episodic memory deficits, emotional disturbances, and walking abnormalities, that gradually interfere with daily life activity (Román, 2003). Currently, there is no approved treatment for cognitive decline so the onset of MID is controlled by the prevention of strokes and controlling risk factors (Baskys and Cheng, 2012).

Microinfarcts are certainly a well-described neuronal pathological finding that can't be detected on gross pathological examination or conventional structural MRI. Cerebral microinfarcts are generally cellular death or tissue necrosis occasionally with a central fluid-filled cavity in microscopic regions (Hachinski *et al.*, 2006; Sonnen *et al.*, 2007; Vinters *et al.*, 2000). When identifying microinfarcts in the early stages of development, they can be observed as the expected acute ischemic appearance of red neurons and losing staining quality. Microinfarcts are usually found in the aging brain. The diversity found in clinical cases most likely became noticed from differences in age and coexisting medical disorders (Sonnen *et al.*, 2011). It is hard to figure out whether or not

microinfarcts lead to the risk of dementia because the frequent occurrence of microinfarcts is also high in brains without dementia and other vascular pathologies including macroinfarcts, WM lesions, or cerebral amyloid angiopathy (CAA) are frequently observed beside microinfarcts within the same brains (De Reuck *et al.*, 2011; del Ser *et al.*, 1990). The location of microinfarcts is often classified as cortical or subcortical which is useful for figuring out the associations with specific diseases. Studies suggest that cortical microinfarct is probably more closely related to dementia than subcortical microinfarcts (Arvanitakis *et al.*, 2011; Troncoso *et al.*, 2008).

Multiple microinfarctions (MMI) in rats set off dementia, periventricular WM harm, hippocampal harm, disturbance of the blood-brain barrier (BBB), elevated inflammatory responses, water channel dysfunction, and causes the glymphatic disorder (Wang *et al.*, 2012; Yu and Venkat, 2019). MMI caused by microsphere-induced embolism was suggested to mimic clinical vascular dementia more closely (Takagi *et al.*, 1995).

## Microspheres

Microspheres are often made from many kinds of natural and synthetic materials. There are microspheres such as glass microspheres, polymer microspheres, and ceramic microspheres that are sold on the market (Karaman *et al.*, 2025; Li *et al.*, 2018). Polymer microspheres including natural and synthetic polymer microspheres are the main carrier materials for preparing microspheres. Some natural polymer microspheres are starch microspheres, albumin microspheres, gelatin microspheres, etc. and synthetic polymer microspheres are polylactic acid microspheres, etc. Solid and hollow microspheres have a huge variety in density and therefore are used differently. Hollow microspheres are usually used as additives to decrease the density of a material and solid microspheres have many applications depending on the material and the size (Sahil *et al.*, 2011).

Microspheres are small spherical particles with diameters that are ranged within the micrometer from 1 to 1000  $\mu\text{m}$ , a dispersion system formed by drug dispersion or adsorption in macromolecule and polymer materials (Karaman *et al.*, 2025; Li *et al.*, 2018). They are mainly prepared into suspensions for injection or oral use. Polystyrene and polyethylene are two of the most common types of polymer microspheres. Polystyrene microspheres are the type of polymer microspheres fit for medical research and biological laboratory experiments. The diameter of microspheres used as emboli in studies (Bralet *et al.*, 1979; Kiyota *et al.*, 1985; Narumi *et al.*, 1986; Sugi *et al.*, 1980) ranged from 15 to 50  $\mu\text{m}$  to develop cerebral ischemia and infarction.

The most pursued objective in anti-cancer therapy is the targeted administration of anti-cancer medications and isotopes. However, a significant drawback of taking these medications systemically is that they have low selectivity for cancer cells and are widely distributed to non-cancerous tissues, which might have harmful side effects on otherwise healthy tissue (Marchal *et al.*, 2015; Perez-Lopez *et al.*, 2022). In order to prevent harmful side effects, new treatments are continuously being found and used for anti-cancer interventions. Theoretically, disease-targeted therapy administration may also lessen the involvement of non-cancerous tissues. Here, selective administration or receptor targeting can direct disease-targeting (Lorscheider *et al.*, 2021). Microspheres have demonstrated their efficacy as trans-arterial drug delivery methods over the past two decades (Rajput and Agrawal, 2010). These microspheres are widely used in both medical and biological science research (Laeschke, 2004; Sinha *et al.*, 2003; Varde and Pack, 2004). Typically, stable or biodegradable microspheres are used to target organs by exploiting circulatory physical barriers (Niu *et al.*, 2017; Osuga *et al.*, 2016; Vaidya *et al.*, 2008; Welling *et al.*, 2023). Therapeutical microspheres have been extensively used for hepatocellular carcinoma (HCC) and hepatic metastases of various solid tumours, such as colorectal, lung, and breast malignancies that spread to the liver (Burrill *et al.*, 2011; Rajput and Agrawal, 2010).

## Animal models for MID

Microspheres have two functions in the research of dementia. They are employed as sophisticated drug delivery devices to evaluate experimental treatments over extended periods of time and to induce distinct types of dementia in animal models, such as vascular dementia or microinfarcts (Venkat *et al.*, 2015).

Endovascular injection of microspheres into the internal carotid artery is a very effective tool in multi-infarct dementia (MID) research for creating experimental animal models. These microembolic spheres physically block penetrating arterioles by lodging in the microvasculature. This results in widespread, multifocal microinfarcts and cerebral hypoperfusion, which effectively mimic human vascular cognitive impairment (Liu *et al.*, 2025; Takagi and Takeo, 2003).

VaD animal models can be separated into vessel occlusion models, multiple infarcts and thromboembolism models, high fat diet (HFD) models, and models using risk factors to induce VaD. The multiple infarcts and thromboembolism models are models that are the most closely connected to clinical.

The vessel occlusion models are the 2 vessel occlusion (2VO) or bilateral common carotid arteries (CCA) occlusion (BCCAO) VaD animal model, the 4 vessel occlusion (4VO), unilateral CCA occlusion (UCCAO) animal model, and bilateral CCA stenosis (BCAS) model. The 2VO seek to model global chronic cerebral hypoperfusion that takes place in aging human and dementia, basically by permanently occluding the bilateral (right and left) CCA (Nanri and Watanabe, 1999). This model is restricted to rats, and is not suitable for use in mouse (Farkas *et al.*, 2007). In the 4VO model, both of the vertebral arteries (VA) and both of the CCAs are occluded on days in a row (Pulsinelli and Brierley, 1979). There are several limitations to the 4VO model as well that include, 2 days process duration, variations in the order of vessel occlusion and various CCA occlusion times (Neto *et al.*, 2005). The UCCAO model is constructed by permanently ligating one of the

CCAs with a thread. The inability to easily identify histological infarcts is a drawback of this model (Yoshizaki *et al.*, 2008). In the BCAS model, the bilateral CCAs are occluded by attaching micro-coils around the CCA with a 30-minute interval between the left and the right CCA during the occlusion. The choice of coil diameter, which may affect mortality and the extent of brain damage, is the primary source of variation in this model (Shibata *et al.*, 2004).

The multiple infarcts and thromboembolism models are the thromboembolic multiple infarction VaD model (Zhang *et al.*, 2013), microspheres induced multiple infarction VaD model (Takagi and Takeo, 2003), and cholesterol crystals induced multiple infarction VaD model (Rapp *et al.*, 2008).

In HFD-induced VaD models, rats are fed with an HFD (Western diet 40 %, Lard based 60 % diet) (Winocur and Greenwood, 2005). Cognitive impairment and oxidative damage caused by HFD were only shown in studies using 60 % Lard-based HFD, not in studies using the regular Western diet of 40 % HFD (Morrison *et al.*, 2010; Pistell *et al.*, 2010).

The risk factors used to induce VaD models are hypertension, diabetes, and age (Bruley-Rosset *et al.*, 1981; Manwani *et al.*, 2014). The most favored rat strain used for studying hypertension in spontaneously hypertensive rats stroke prone (SHRSP) is SHR (Yamori *et al.*, 1976). The diabetic mouse models are type one diabetes mellitus (T1DM) and type two diabetes mellitus (T2DM) rat and mouse models (King, 2012).

The MMI model in Wistar rats was constructed by injecting 700–900 microspheres that were 48  $\mu\text{m}$  in diameter into the right internal carotid artery (ICA) (Miyake *et al.*, 1993; Takagi and Takeo, 2003). The neurological deficit was the sum of symptoms such as paucity of movement, truncal curvature, and forced circling during locomotion (Fukatsu *et al.*, 2002).

The MMI model in Wistar rats of Wang *et al.* (2020) was constructed by injecting about 1000 microspheres that were  $49.0 \pm 4.0 \mu\text{m}$  in diameter. TUNEL staining was conducted for

histological analysis to identify apoptosis cells in the hippocampus.

## CONCLUSION

Multi-infarct dementia is one of the most common causes of dementia. The aetiology of MID dementia is ischaemic or hemorrhagic cerebrovascular disease, cardiac and circulatory disorders. The best way to prevent MID is to control the risk factors. There are several different medication lines that can help slow the progression of MID. The development of microspheres falls under the category of targeted drug delivery, which has numerous advantages, including increased bioavailability through improved solubility and sustained drug release, as well as increased drug efficacy and reduced adverse effects when the drug is formulated as microspheres. Formulating the drug as microspheres increases patient compliance and reduces the dosing frequency. This technique is especially flexible since it can encapsulate both hydrophilic and hydrophobic medications in microspheres. It may also be investigated to employ microspheres in conjunction with other drug delivery methods like liposomes and nanoparticles.

## CONFLICT OF INTEREST

The author declares that this article content has no conflict of interest.

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