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ABSTRACTS

Abstracts from the 46th Annual Meeting of Japanese Society for Microcirculation

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Keynote Lecture | KL | Presidential Lecture of the 46th annual meeting of the Japanese Society for Microcirculation

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Last year, in September 2020, due to the COVID-19 pandemic, the conference was a hybrid of venue type and WEB type, but the 45th annual meeting of the Japanese Society for Microcirculation was held very magnificently under the President of annual meeting, Dr. Yuji Naito (Kyoto Prefectural University of Medicine). At that time, I was elected as the President of the Japanese Society for Microcirculation as the second term from 2020, and for the first time, I had the opportunity to give a lecture of President of the society. This time, I am deeply grateful to Prof. Masato Matsuo (Kanagawa Dental University), the President of the 46th annual meeting of the Japanese Society for microcirculation (Yokohama) for giving me the opportunity of the Presidential lecture again.

The history of the Japanese Society for Microcirculation is about 50 years, counting from the study group in its early days. In 1971, Dr. Masaharu Tsuchiya established "Gathering of Microcirculation Researchers" in consultation with founders, Dr. Takehiko Azuma, Dr. Makishige Asano, Dr. Yoshio Mishima, and Dr. Ryu Nakayama. This workshop was a forum for exchanging opinions on the microcirculatory system in various parts of the body. Held from the first "Gathering of Microcirculation Researchers" (February 14, 1976) to 26th, during that time, Tokyo International Symposium on Microcirculation (1981, at Sasagawa Hall) and Symposium on INTRAVITAL OBSERVATION OF ORGAN MICROCIRCULATION (1983, at Tokai Univ. Alumni Hall) were held. Then, such a study group was developed into the "Japanese Society for Microcirculation" on February 16, 1985. In 1987, Prof. Tsuchiya, as a President, held the 4th World Congress for Microcirculation (1987. 7. 26- 8. 2, Keio Plaza Hotel, Tokyo) with 440 foreign delegates from 27 countries and 500 domestic delegates. After Prof. Tsuchiya passed away, Prof. Hiromasa Ishii was appointed as the second President in 2001, and then, Prof. Makoto Suematsu was appointed as the third President in 2008 and held the 10th World Congress for Microcirculation in Kyoto (Kyoto International Conference Center, Kyoto) with 240 delegates from overseas (30 countries) and 164 delegates from Japan. On March 26, 2016, I was appointed as the fourth president of the Japanese Society for Microcirculation and currently performing the second term mission.

Life science research in the coming era is an area that covers a broad range from basic to clinical, such as microcirculatory science. For this purpose, the activities of this academic society are extremely important, encompassing many interdisciplinary areas such as basic medicine, clinical medicine, engineering, pharmacy, agriculture, information science, and sociology, and between researchers in Japan and abroad. It is necessary to foster the next generation while promoting exchanges and joint research. It is also important to carry on new academic challenges positively and promptly while inheriting the brilliant flow established by seniors and respecting tradition. Such a trend should not be stopped, even under the COVID-19 pandemic, but rather promoted further. In fact, it is said that the new coronavirus infection targets vascular endothelial cells, which is a major stage of microvascular research.

In September 2022, Director Han will host the 12th World Congress for Microcirculation in Beijing, China, and I hope that many researchers from Japan will participate and play an active role and talk about the recent academic and clinical progress in the field.

Special Lecture | SL | Ameliorative effect and mechanism of Traditional Chinese Medicine on febrile disease—Discussion on the mechanism of TCM in treating COVID-19

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COVID-19 has infected 8.3 million people worldwide, leading to 1.8 million death. However, in China, only 96 thousand people were

infected with around 4 thousand and 700 death. This was partly due to the usage of TCM in the treatment of COVID-19.

In the theory of TCM, diseases caused by infection and characterized by fever are called febrile disease. "Treatise on Febrile Diseases" (Shang Han Lun), which was written in Han dynasty, recorded many Traditional Chinese medicine formula. In the Ming and Qing dynasty, Warm Disease Theory (Wen Bing Xue) was developed. In this theory, infectious disease is divided into four stages as Wei, Qi, Ying, and Xue. The disease is treated according to its stage.

In the early stage of infection, virus invades respiratory tract and digestive tract, which belongs to Wei stage. Yin-Qiao-San and Huo-Xiang-Zheng-Qi-San could be used. The replication of virus causes the entering of alarmin and LPS into blood through the damaged intestinal epithelium, which then bind to TLR4 receptor and result in release of inflammatory factors, the interaction between white blood cells and endothelial cells, leading to fever, cough, and dyspnea. This belongs to Qi stage, and Ma-Xing-Shi-Gan-Tang could be used. Cerebral microvascular leakage caused coma, thready pulse and crimson tongue belongs to Ying stage; damage of blood vessel basement membrane leading to hemorrhage and thrombus belongs to Xue stage. Xi-Jiao-Di-Huang-Tang could be used.

Using microcirculation observation system, the speaker investigated the effects and mechanisms of Qing-Fei-Pai-Du-Tang, Ma-Xing-Shi-Gan-Tang, Qing-Ying-Tang, Sheng-Mai-San, and catalpol, the major effective ingredient of Xi-Jiao-Di-Huang-Tang, in treating LPS induced microcirculation disturbance.

Symposium 1

Novel Treatment Strategies based on Microcirculatory Disturbance in Brain Disorders

SY1-2 | The impact of obesity on brain infarction

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Obesity, excessive accumulation of adipose tissue, is epidemiologically proven to be related with many diseases, such as diabetes, dyslipidemia, hypertension, cardiovascular disease, and cancer.

In terms of the influence of obesity on incidence of brain infarction, Japanese cohort study shows that obesity increases the risk of all types of infarction in male and lacunar/atherosclerotic infarction in female. We have experimentally estimated the impact of obesity on outcome of brain infarction using 5- to 7-week-old leptin-knockout mice (*ob/ob*) before development of diabetes.

Leptin, one of adipokines released from adipose tissue, suppresses appetite, acting on the satiety center in hypothalamus. Therefore, *ob/ob* mice gain weight due to overeating.

In our experiment, wild type (C57BL6/J), *ob/ob*, and *ob/ob*+Lep (*ob/ob* with reconstitution of leptin using a subcutaneous infusion pump, mimicking human obese population whose leptin level is often high because of its resistance) were prepared. Following 30 minute middle cerebral artery occlusion and reperfusion using silicone-coated nylon thread, leukocyte/platelet recruitment, infarction volume, BBB (blood-brain barrier) disruption, edema, and cytokine amount were measured. These indicators significantly elevated in *ob/ob* and *ob/ob*+Lep regardless of leptin. These results were accompanied by elevation of MCP-1 and IL-6 and were remarkably reduced by anti-MCP-1 antibody. These findings indicate obesity per se can induce more severe outcome after ischemic insult and cytokines such as MCP-1 may play some roles in the exacerbation. Adipose tissue contains several cell types, and it is recently recognized not only as storage organ, but also as endocrine organ. And many vitro data show that activated sympathetic nervous system can promote the secretion of many cytokines from adipose tissue. Taken together, the brain insult may induce the sympathetic stimulus leading to the secretion of adipose-derived proinflammatory cytokines, which in turn may exaggerate the brain injury. The modulation to this "brain-systemic axis" may be a future therapeutic target.

SY1-3 | Cerebral ischemia and inflammation

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Ischemic stroke triggers an inflammatory reaction in the affected area, which progresses for days to weeks after the onset of symptoms. There is evidence that such inflammatory processes contribute to the progression of ischemic brain injury, worsen the tissue damage, and exacerbate neurologic deficits. Therefore, interventions aimed at suppressing postischemic inflammation offer attractive therapeutic strategies for human stroke, with a potentially wide therapeutic window. CD36 is a type-B scavenger receptor expressed in microglia, macrophages, and endothelial cells, which is involved in inflammatory signaling. CD36 recognizes several ligands and may interact with toll-like receptors to activate inflammatory signaling through the transcription factor NF-κB.

Focal cerebral ischemia upregulates CD36 in the ischemic brain, and CD36-null mice have smaller infarcts and better neurologic outcomes after focal ischemia. CD36 plays a key role in focal cerebral ischemia because it is essential for postischemic NF-κB activation and for the full expression of the cellular and molecular signals driving postischemic inflammation.

Furthermore, these inflammatory mediators, under certain conditions, can confer tolerance to cerebral ischemia. Administration of LPS 24 hours before middle cerebral artery (MCA) occlusion reduced ischemic brain injury and prevented the dysfunction in cerebrovascular regulation induced by MCA occlusion. New strategies that create tolerance to selected brain antigens also offer the potential of considerable neuroprotection.

In this symposium, I would like to review the basic cellular and molecular features of postischemic inflammation, focusing on recent advances and insights on the potential mechanisms by which such inflammation influences stroke outcome.

SY1-4 | Neurovascular unit and astroglia: a prime target of brain diseases

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Normal brain function is dependent on microcirculation which provides continuous supply of glucose and oxygen, indispensable energy substrates. In addition to brain microvessels and neurons, glial cells play pivotal roles in the regulation of brain microcirculation and metabolism. Astroglia are one of the three types of glial cells in the brain: astroglia (astrocytes), oligodendroglia (oligodendrocytes), and microglia. Astroglia are the most abundant cells in the human brain and outnumber neurons by a factor of 1.4 in the human cerebral cortex. In addition, their unique anatomical location, which is interposed between neurons and cerebral microvessels and was depicted more than 100 years ago in a sketch by a legendary neuropathologist, Santiago Ramón y Cajal, has been attracting the attention of many neuroscientists. Neurons, microvessels and astroglia form the "neurovascular unit (NVU)," a conceptual framework that was originally used to better understand the pathophysiology of cerebral ischemia. Now, the NVU is a tool that can be used to understand normal brain physiology and the pathophysiology of numerous neurological disorders. Therefore, NVU could be a prime target of brain disorders like ischemia, demyelination, neuroinflammation, or neurodegeneration. In fact, the metabolic responses of astroglia in the NVU can be either protective or deleterious. This review focuses on three major metabolic compartments: (i) glucose and lactate; (ii) fatty acid and ketone bodies; and (iii) D- and L-serine. Both the beneficial and the detrimental roles of compartmentalization between neurons and astroglia will be discussed. A better understanding of the astroglial metabolic response in the NVU is expected to lead to the development of novel therapeutic strategies for diverse neurological diseases.

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Symposium 2

Role of Microcirculation in Gastrointestinal Inflammation and Carcinogenesis

SY2-2 | The role and potential mechanisms of heme oxygenase-1 on ischemia/ reperfusion-challenged intestinal injury in mice

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Aim: Intestinal ischemia/reperfusion (I/R) injury is a complex, multifactorial, pathophysiological process with high morbidity and mortality, leading to serious difficulty in treatment. Although the mechanisms involved in the pathogenesis of intestinal I/R injury have not been fully elucidated, it is generally believed that oxidative stress and subsequent inflammation play an important role. Heme oxygenase (HO) is the rate-limiting enzyme in the catabolism of heme, followed by production of CO, biliverdin, and free iron. In particular, HO-1 (an inducible form) is believed to confer cytoprotection by inhibiting inflammation, oxidation, and apoptosis, and maintaining microcirculation. Therefore, we investigated the role and potential mechanisms of HO-1 on modulation of inflammatory responses in I/R-challenged intestinal injury. In addition, the role of BTB and CNC homolog 1 (Bach1), which is a transcriptional repressor of HO-1, nuclear factor-erythroid 2-related factor 2 (Nrf2), which has been known to be a transcriptional factor of HO-1, and CO, one of the by-products of heme degradation by HO, were investigated in this study.

Methods: Intestinal damage was induced by clamping the superior mesenteric artery for 45 min followed by reperfusion in male wild-type mice (C57BL/6), Bach1 deficient mice, and Nrf2 deficient mice. CO-releasing molecule (CORM) was intraperitoneally administered before induction of ischemia. Subsequently, intestinal damages were evaluated macroscopically, histologically, and biochemically 4h following reperfusion.

Results: Luminal inflammatory markers such as luminal protein and hemoglobin, tissue levels of TNF-alpha and KC, and subsequent PMN accumulation were significantly elevated in I/R-challenged small intestine of WT mice. These changes were significantly attenuated in Bach1 deficient mice or treatment of CORM and obviously deteriorated in Nrf2 deficient mice. In addition, the treatment with HO-1 inhibitor resulted in the reverse of these attenuations in I/R-challenged small intestine of Bach1 deficient mice.

Conclusions: These findings indicate that HO-1 exhibits protective effects against intestinal I/R injury.

SY2-3 | Role of prostaglandin E2 related pathways in gastric adenocarcinoma

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Background and Aim: Prostaglandin (PG) E2 promotes gastrointestinal carcinogenesis and tumor progression. The total amount of biologically active PGE2 in tissues is determined by a balance of PG biosynthesis and degradation pathways, which involve the PG transporter (PGT) and 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a catabolic enzyme for biological inactivation of PGE(2). We investigated PGT and 15-PGDH in gastric adenocarcinoma by determining its expression pattern and examining associations of PGT and 15-PGDH with prognosis and tumor angiogenesis.

Methods: 15-PGDH and PGT expression was determined by immunohistochemistry in advanced gastric adenocarcinoma specimens obtained from patients who underwent surgical resection. Angiogenesis in the tumor tissue was evaluated by counting the number of microvessels. Human gastric carcinoma cell lines were used for in vitro study. The Ethics Committee of Osaka City University approved this study.

Results: Multivariate analysis revealed reduction in 15-PGDH expression to be an independent predictor of poor survival. The proportion of Ki67-positive cells in 15-PGDH-negative adenocarcinoma was higher than that in 15-PGDH-positive adenocarcinoma. Negativity for PGT expression was also an independent poor prognostic factor. There were more microvessels in PGT-negative tumors than in PGT-positive tumors. Use of specific siRNA to silence 15-PGDH or a specific inhibitor of 15-PGDH enhanced cell proliferation in the gastric cancer cell line AGS. Transfection of AGS and MKN7 gastric cancer cells with PGT-specific siRNA led to increased VEGF mRNA and protein expression accompanied by increased PGE2 in the culture media.

Conclusion: These findings suggest that reduction in 15-PGDH or PGT expression is an independent predictor of poor survival in gastric adenocarcinoma.

Symposium 3

Role of Biomedical Engineering for Understanding Cerebral Microvascular Diseases

SY3-1 | Neural regulation of cerebral microvasculature, and its association with mastication

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In the brain microcirculation, the implications of neural regulation are complex. In addition to sympathetic and parasympathetic nerves that regulate cerebral surface arteries (extrinsic control), nerves inside the brain regulate microvasculature in the brain parenchyma (intrinsic control). In particular, vasodilative regulation by basal forebrain-derived cholinergic fibers, which is important for cognitive function, is of particular interest in relation to dementia. Although it is not fully understood how these various nerves are involved in physiological regulation of cerebral blood flow under various conditions, it must be important for brain function to receive both extrinsic and intrinsic innervation, especially diverse and potent vasodilative innervation.

Recently, deep brain stimulation targeting the basal forebrain cholinergic nucleus (nucleus basalis of Meynert: NBM) has been clinically examined for a treatment of Alzheimer's disease. In contrast, lifestyle interventions such as diet and exercise have been shown to improve cognitive function in the elderly with mild cognitive impairment. We hypothesized that daily activities including chewing may stimulate the NBM. rCBF increases during mastication in humans; however, the mechanism has not been clarified yet. We investigated the neural mechanism of rCBF increase associated with masticatory-like jaw movement in rats, focusing on the NBM. Our results showed that activation of vasodilator neurons in the NBM contributes, at least in part, to the rCBF increase associated with jaw movement and that activation of NBM is triggered by commands from masticatory motor cortex, independent of feedback from contractile muscles or pattern generators.

In this lecture, I will outline the characteristics of the neural regulation of cerebral microvasculature and introduce our recent study on increased cerebral blood flow associated with mastication.

References

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SY3-3 | Imaging of cerebral microcirculation and expectations for biomedical engineering

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Cerebral microvessels are covered with the end feet of astrocytes and are connected to neurons to form a functional complex, the neurovascular unit, which is surrounded by glial cells. Control of cerebral blood flow (CBF) is coupled with brain metabolism, and gross CBF is mainly controlled by dilation/constriction of the arteries and arterioles. On the other hand, regional microcirculation, including capillary flow, may be regulated by signals from nearby cells to meet the energy demands of the parenchyma. To elucidate the regulatory mechanisms of the cerebral microcirculation, we observed blood flow in microvessels in the cerebral cortex through a closed cranial window chronically implanted in experimental animals *in vivo*. Three-dimensional capillary flow maps were created from measurements of transmitted light from the subcortical region using our own software, KEIO-IS1, based on mean transit time (MTT) analysis. This system enables repeated longitudinal measurements of CBF in the same area of mouse brain through the cranial window over a long period. The movements of intravenously administered fluorescence-labeled red blood cells (RBCs) were automatically analyzed using our software KEIO-IS2, enabling two-dimensional mapping and evaluation of temporal changes in the velocity of RBCs in each capillary. In addition, spatiotemporal changes in the diameter of pial arteries, penetrating arteries, and capillaries were analyzed using confocal and two-photon microscopy. Using these methodologies, we evaluated microcirculatory changes after stroke or cerebral spreading depression, and we identified a distinctive mechanism of CBF regulation by astrocytes using optogenetics. These techniques are powerful tools for exploring the behavior and/or interaction of different cell types. Hyporemic ischemia may induce regional hypoxia and neuronal dysfunction, resulting in various vascular diseases, failure of autoregulation, head trauma, dementia, and so on. Studying the mechanisms associated with microcirculatory regulation and cellular interactions under pathological conditions may lead to the identification of new therapeutic targets.

(Animal use and experimental protocols (No. 09058) were approved by the Animal Ethics Committee of Keio University Medical School, and all experimental procedures were in accordance with the university's guidelines for the care and use of laboratory animals.)

Symposium 4

China-Japan Joint Symposium of Microcirculation "Qi-Blood"

SY4-3 | LPS transport in the small intestine

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Lipopolysaccharides (LPS), well-known bacterial factor inducing microcirculatory disturbances and organ injuries, are mainly originated from the intestinal lumen, while the mechanism of LPS entry into the systemic circulation is unclear. Circulating LPS causes sepsis at high dose, but also induces metabolic syndrome with low grade inflammation. We investigated LPS transport mechanisms and the effects of exogenous glucagon-like peptide-2 (GLP-2) on LPS transport, multiple organ injuries with critical illness, and fatty liver.

In Ussing chambered rat jejunal mucosa, luminal LPS rapidly appeared in the serosal solution only with luminal oleic acid and taurocholate (OA/TCA) present, inhibited by the inhibitors of lipid raft, CD36, and dynamin, or by serosal GLP-2. *In vivo*, perfusion of FITC-LPS with OA/TCA rapidly increased FITC-LPS appearance into the PV, followed by a gradual increase in FITC-LPS into the lymph. Rapid PV transport was inhibited by the lipid raft inhibitor or CD36 inhibitor, whereas lymphatic transport was inhibited by chylomicron synthesis inhibition. The stable GLP-2 analog teduglutide (TDG) iv acutely inhibited PV FITC-LPS transport via NO and VIP pathways. *In vivo* confocal microscopy in mouse jejunum confirmed intracellular FITC-LPS uptake with no evidence of paracellular localization. Cerulein-induced acute pancreatitis induced pro-inflammatory cytokine expressions in the lung, liver, and ileum with increased PV LPS levels, while TDG treatment reduced these changes without the effect on pancreatitis. High-fat diet increased PV LPS levels and hepatic TNFα expression, the effects reduced by the FFA3 agonist in drinking water which releases GLP-2 from L cells.

These results suggest that luminal LPS traverses the small intestinal barrier physiologically during fat absorption via lipid raft, CD36, and caveolae-mediated mechanisms, followed by predominant transport into the PV, and that GLP-2 inhibits LPS uptake into the PV. LPS-related systemic inflammatory diseases may be treated by the reduction in intestinal LPS entry via GLP-2 pathway.

Free Paper | F-5 | Hair movement-induced lymph formation in the mouse

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Peripheral lymph formation is associated mainly with mechanical movement of the tissue, such as arterial pulse, vibration, and massage. Hair is an appendage of the skin and easily moves by contacts and winds. Recently, it was reported that there is functional connection between initial lymphatic and hair follicle growth, and distribution of the initial lymphatics correlates that of the hair follicles. To the best of our knowledge, however, no investigation was carried out to evaluate effects of hair movement on lymph formation. Thus, in this study, a relationship between hair movement and expansion of a lumen of the initial lymphatics was investigated in the murine skin. Male ICR mice were used in this study (approval no. 18083). Right and left sides of the murine back skin were adopted to make histological sections. In one side of the back, hairs were stiffened along the fur with glue and in the other side, they were stiffened reversely. Longitudinal sections were obtained from the skins and immunohistochemically stained by anti-LYVE1 Ab to detect the initial lymphatics. Then, luminal area was measured in each lymphatic. The luminal area was significantly larger in reversely stiffened skin than in the skin stiffened along the fur. This finding supports the idea that hair movement increases luminal volume in the initial lymphatics accompanying the hair follicles, and this morphological change is a result of luminal filling. According to our previous studies, relationship between frequency of hair movement (f) and the amount of lymph formation (Q) follows the equation $Q = 2Af\{1-\exp(-1/2tf)\}$, where A and t are constants (Microcirculation 27;e12606;2020). In conclusion, it was confirmed that hair movement increases luminal area of the initial lymphatics accompanying the hair follicles and suggested that the hair movement enhances lymph formation in the skin.

F-6 | The changes of gingival vascular network using *Jixueteng* in a mouse periodontitis model

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Objective: *Jixueteng* is a traditional Chinese medicine to improve and activate blood circulation and used for the treatment of blood deficiency. The aim of this study was to investigate the possibility of *Jixueteng* as a preventive therapy drug for the periodontitis. *Jixueteng* is a traditional Chinese medicine that improves and activates blood circulation. Therefore, it is used for the treatment of blood deficiency and rheumatalgia. In the present study, we determined the efficacy of *Jixueteng* for *P. gingivalis*-induced alveolar bone loss and gingival circulatory failure using a mouse model.
Materials and methods: Four-week-old C57BL/6N mice were randomly divided into three groups, which consist of 18 mice per group. After the bacterial infection, six mice were extracted from each group and examined a gingival blood flow. The reaction and vascular changes of vessels in experimentally induced chronic inflammation of the periodontal tissues were investigated using corrosion resin casts and scanning electron microscopic examination. In addition, horizontal bone loss around the maxillary molars was assessed morphometrically. The distance from the cementoenamel junction to the alveolar bone crest was measured at seven buccal sites per mouse.
Results: *P. gingivalis*-infected mice showed reduction in gingival reactive hyperemia remarkably. The morphological degeneration of vessels was also observed in the number of vascular networks and abnormality of the vascular lumen caused by *P. gingivalis* infection. The induction of alveolar bone loss was more prominent in *P. gingivalis* infection group in 4 weeks after last infection. Alveolar bone loss was significantly lower in the administration of *Jixueteng* than that of *P. gingivalis* infection. *P. gingivalis*-induced alveolar bone loss was markedly suppressed by administration of *Jixueteng*.
Conclusion: These results suggest that *Jixueteng* may improve gingival microcirculation and be useful for oral health.

F-7 | Numerical simulation of alveolar bone regeneration-reproduction of the regeneration process in extraction sockets-

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In recent years, the number of people suffering from dental diseases has been increasing due to the aging of the population, and dental regenerative medicine, such as implant treatment, is becoming more and more active. In implant treatment, the bone of the jaw, called alveolar bone, regenerates and the implant is fixed in place. The implant and alveolar bone do not bond properly, leading to treatment errors. In this study, we aim to reveal the mechanism of bone regeneration and to contribute to dental regenerative. In this study, we developed an equation that takes into account external stimulation and calcium transport from blood vessels, which are factors in bone regeneration, and analyzed it in a coupled manner using particles. We were able to visualize the process of bone regeneration in the entire region over a period of 90 days from the state immediately after tooth extraction. As a result of comparing the analysis results with animal experiments, qualitative characteristics of bone structure and blood vessels were consistent.