The third Special Topic of papers on new regulatory mechanisms in the coronary microcirculation is focused on the control of coronary vasomotor tone. Papers with both a basic scientific and clinical orientation are included, because in the aggregate, the studies show the importance of the coronary microcirculation from both physiological and pathophysiological perspectives. Several of the papers were presented at an international workshop on Integrated Control of Pressure and Blood Flow in Coronary Microcirculation as a component of the European Working Group on the Microcirculation. Importantly, all the papers in this Special Topic represent original contributions by the authors. As a component to this collection of papers, the Editors have included a Medical Editorial entitled, “Why should we study the coronary microcirculation” as a foreword, which further shows the clinical perspective to the importance of this area.

Six of the papers in this Special Topic are basic in nature, but they examine a variety of physiological and pathophysiological questions. Graves and co-workers (4) have reported the putative role for a chloride channel in mediating smooth muscle contraction in small coronary arteries. These investigators further suggested that nitric oxide normally suppresses this chloride channel in vascular smooth muscle. Although the investigators in this study did not use electrophysiological techniques to unequivocally ascertain the existence of chloride channels, their results are very suggestive of such heretofore unappreciated ionic regulation of coronary vascular tone. Clarke and Fuchs (2) examined a different aspect of ion channel regulation of coronary vascular tone; namely, changes in the ion channels that accompany heart failure. These investigators reported that microvessels from failing hearts (myopathic hamsters) relied on dilation mediated via charybdotoxin-sensitive mechanisms more than those from normal hearts. Although charybdotoxin is not specific for a single potassium channel, the results show that heart failure is associated with aberrations in coronary vascular regulation. Whether the shift in ionic mechanisms is the cause or the effect of heart failure is still an open question. Similar to the paper by Graves et al. (4), electrophysiological confirmation of dilator mechanisms would be of interest. Heart failure is associated with increased production of the vasodilator peptide adrenomedullin. Terrata and colleagues (8) reported on the mechanism of coronary arteriolar vasodilation to adrenomedullin using tissue from patients with coronary artery disease. In contrast to many animal tissues, human coronary arterioles do not rely on activation of cGMP for adrenomedullin-induced vasodilation, although nitric oxide production is involved. Also in contrast to animal models, adrenomedullin-induced dilation was reduced in patients with hypertension. These findings underscore the species variability in vascular responses and highlight the need to link basic findings to the human condition.

Zhang et al. (9) reported that reactivity of isolated coronary microvessels to adenosine is modulated by intraluminal pressure. Specifically, reductions in perfusion pressure increased the sensitivity to the vasodilatory effects to adenosine. These investigators further speculated that this effect contributes to dilation by adenosine during coronary hypoperfusion. Merkus et al. (5) observed another new action of adenosine on constriction of coronary arterioles in vitro and in situ to endothelin-1. Exposure of isolated or in situ microvessels to adenosine greatly abrogated constriction to endothelin-1. The importance of this mechanism is that it offers insight into mechanisms by which the coronary microcirculation may become refractory to the effects of constrictors. Moreover, this response was mimicked by ischemic preconditioning, which is thought to be mediated by increases in adenosine during myocardial ischemia. Dörge and co-workers (3) reported striking differences in flow-function relationships caused by a stenosis or microvascular embolization. After production of a stenosis or after injection of microspheres, the acute flow function relationships were similar. However, function progressively deteriorated over time in the embolization group versus improvement in func-

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ion in the stenosis group. The authors have surmised that the micro areas of ischemia may incite inflammatory processes and cause the expression of cytokines leading to the deterioration of function. The interesting new concept promoted by the paper by Dröge et al. (3) is that flow-function relationships have been thought of as linear or curvilinear functions for about two decades, but Dörgé et al. call into question such traditional interpretations.

Three papers in the clinical sciences report a variety of observations, but there is a general theme linking them together: studies of the microcirculation can provide insight into the pathophysiology of ischemic heart disease. Sambuceti and colleagues (6) reported the observation that perfusion pressure directly modifies the total perfusion area of an artery being studied. The impact of this observation focuses on whether following an intervention, such as angioplasty, after which coronary perfusion pressure downstream from the remodeled lesion increases, the resulting increase in flow is due to enhanced myocardial perfusion per unit mass or is it due to an increase in the perfusion territory? This caveat is an important qualifier to the interpretations of numerous clinical studies. Spyrou and colleagues (7) made an equally important observation that affects interpretations of flow responses following angioplasty procedures. Specifically, these investigators found that the coronary flow reserve increased progressively over the course of months following an angioplasty procedure. This implies remodeling in the downstream microcirculation associated with the increase in perfusion pressure, which appears to offer a benefit to the patient. Finally, Buffon et al. (1) identified a role of the coronary microcirculation in myocardial ischemia. In syndrome X patients without significant coronary disease, increasing metabolic demands during pacing resulted in the production of lipid peroxides and conjugated dienes products of ischemia. Whether or not syndrome X patients have ischemic episodes has been actively debated in the literature for a number of years, but these findings provide strong evidence for myocardial ischemia in this condition. Each of these clinical studies provides important new insights into the function of the coronary microcirculation of patients with disease.

Despite the new concepts and, of course, the new questions promulgated by the collection of these papers, there are still many unresolved issues regarding control of the coronary microcirculation. For example, how is flow coupled to metabolism and how do the myriad of endogenous vasoactive agents interact to regulate coronary vasomotor tone? Perhaps with some of the new insights gleaned from the results in this Special Topic, new investigations will lead us toward a more complete understanding of coronary vascular control under physiological and pathophysiological conditions.

REFERENCES