



## Commentary

## Vascular Spasm: A Newly Unraveled Cause for Cardiovascular Adversity of Proteasome Inhibition



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Given the vital role of the ubiquitin-proteasome system (UPS) in propelling the cell division cycle and sustaining cell survival, UPS inhibition is being intensively explored as a therapeutic strategy for treating malignancy, which is surely fueled by the impressive efficacy demonstrated by proteasome inhibitors bortezomib (BZM) and carfilzomib (CFZ) in treating multiple myeloma (MM) ((Chen-Scarabelli et al., 2017) and references therein). However, severe cardiovascular adverse effects such as sudden death, arrhythmia, angina, heart failure, and pulmonary hypertension to name a few, have been observed in MM patients treated with regimens containing BZM or CFZ ((Enrico et al., 2007, Chen-Scarabelli et al., 2017) and references therein). Most cardiovascular complications are reversible if the use of proteasome inhibitors is timely terminated but prematurely ceasing proteasome inhibitor treatment due to severe unintended effects will obviously limit the clinical benefit of these efficacious agents. Hence, it is extremely important to achieve a better understanding of the underlying causes as it can guide the development of targeted strategies and measures to prevent and manage the life-threatening cardiovascular adverse effects.

Prior experimental studies have demonstrated that genetic and pharmacological inhibition of the proteasome in the cardiomyocyte compartment exacerbates acute myocardial ischemia/reperfusion injury and the maladaptive cardiac remodeling and heart failure induced by acute pressure overload (Tang et al., 2010; Tian et al., 2012) through perturbation of protein quality control and exacerbation of proteotoxicity while chronic cardiac proteasome functional insufficiency has been established to play a major role in the genesis and progression of cardiac proteinopathy (Li et al., 2011), pressure overloaded maladaptive cardiac remodeling and failure (Ranek et al., 2015), and diabetic cardiomyopathy (Li et al., 2017). These prior reports certainly presented a compelling argument for a notion that derangements caused by acute or sustained proteasome inhibition in the cardiomyocyte compartment contribute to at least some of the cardiovascular complications occurred in MM patients receiving proteasome inhibitor-containing chemotherapies.

Proteasome malfunction was also implicated in vascular pathology such as atherosclerosis as well as vascular ageing and pharmacologically induced chronic proteasome inhibition was shown to cause coronary artery constriction, hasten high fat diet induced atherosclerosis, and

result in restrictive cardiomyopathy in pigs (Herrmann et al., 2007; Herrmann et al., 2013), suggesting that chronic vascular injury and remodeling could also be a mechanism underlying some of the cardiovascular adversity induced by treatment with a proteasome inhibitor. However, many of the acute cardiovascular complications such as sudden death, arrhythmia, and myocardial ischemia occurred during or shortly after CFZ infusion are quite difficult to explain with the long term cardiovascular toxicities observed so far in animal experiments. Now, this situation is likely changed for good.

A recent report by Chen-Scarabelli et al. describes a timely study that employed *ex vivo* perfused isolated rabbit hearts and aortic tissue strips to assess the effect of acute administration of CFZ on coronary resistance, vascular tone and reactivity (Chen-Scarabelli et al., 2017). Their experiments revealed that acute perfusion of CFZ could raise coronary perfusion pressure and resting vasoconstricting tone and sensitize the spasmogenic effect of noradrenaline, angiotensin II, and potassium chloride; preincubation with CFZ antagonized the anti-spasmogenic activity of nitroglycerin and nifedipine and strikingly decreased the vasodilating effect of acetylcholine by over 50%, providing the first experimental evidence that CFZ acutely impairs vasodilation through an endothelium-dependent mechanism. These novel findings present a potentially new mechanism for the clinically observed adverse cardiovascular effects of CFZ, especially those with an acute presentation. It is conceivable that coronary spasm triggered by CFZ could directly cause myocardial ischemia and thereby arrhythmia, cardiac sudden death, and even acute heart failure whereas the consequence of repeated episodes of coronary spasm could be chronic ischemic heart disease-like, impairing both cardiac contractility and relaxation. The endothelium-dependent nature of CFZ's spasmogenic effect points to a direction for further elucidation of the molecular basis. Through catalyzing the synthesis of the potent vasodilator nitric oxide (NO), endothelial NO synthase (eNOS) plays an important role in regulating vascular tone and reactivity. Notably, it has been shown by at least one earlier study that proteasome inhibition suppresses eNOS activity *via* promoting protein phosphatase 2A-mediated dephosphorylation and thereby inactivation of eNOS (Wei and Xia, 2006), corroborating the spasmogenic effect of CFZ reported by Chen-Scarabelli et al. (Chen-Scarabelli et al., 2017).

The study by Chen-Scarabelli et al. only tested CFZ (Chen-Scarabelli et al., 2017); hence, the conclusion drawn may or may not be applicable

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to proteasome inhibition in general. It will be interesting and important to test whether other proteasome inhibitors (e.g., BZM) would yield the same acute effect and whether the effect occurs *in vivo* and can be mitigated by repeated and intermittent administration of a proteasome inhibitor. Meanwhile, proper validation of the findings in clinical settings is urgently needed because, if validated, they would demand reconsideration of CFZ's contraindications; by current guidelines, the population of MM patients with high-risk of severe cardiovascular complications, such as myocardial infarction or unstable angina, heart failure, and systemic and pulmonary hypertension are eligible for CFZ treatment. Regardless, this study certainly adds additional evidence for taking the precaution that cardiovascular risk factors and coexisted cardiovascular conditions must be thoroughly diagnosed and effectively managed before initiating CFZ infusion.

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#### Disclosure

None.

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